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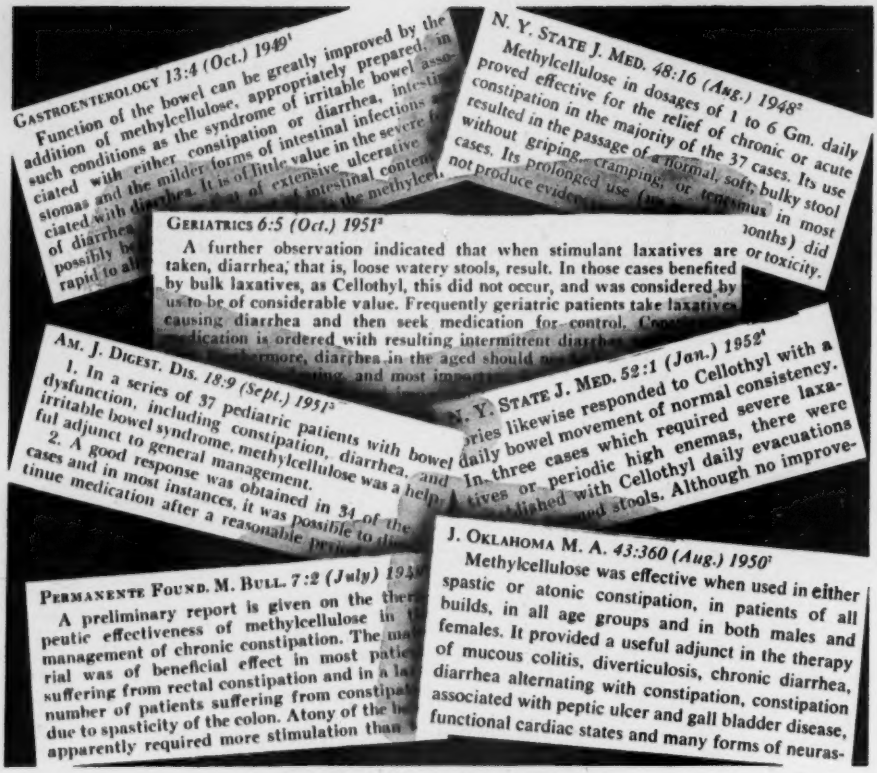
GASTROENTEROLOGY 13:4 (Oct.) 1949[1]
Function of the bowel can be greatly improved by the addition of methylcellulose, appropriately prepared, in such conditions as the syndrome of irritable bowel associated with either constipation or diarrhea, intestinal stomas and the milder forms of intestinal infections associated with diarrhea. It is of little value in the severe forms of diarrhea, of extensive ulcerative intestinal content possibly by the methylcel rapid to al
N. Y. STATE J. MED. 48:16 (Aug.) 1948[2]
Methylcellulose in dosages of 1 to 6 Gm. daily proved effective for the relief of chronic or acute constipation in the majority of the 37 cases. Its use resulted in the passage of a normal, soft, bulky stool without griping, cramping, or tenesmus in most cases. Its prolonged use (months) did not produce evide or toxicity.
GERIATRICS 6:5 (Oct.) 1951[3]
A further observation indicated that when stimulant laxatives are taken, diarrhea, that is, loose watery stools, result. In those cases benefited by bulk laxatives, as Cellothyl, this did not occur, and was considered by us to be of considerable value. Frequently geriatric patients take laxatives causing diarrhea and then seek medication for control. Con dication is ordered with resulting intermittent diarrhea. rmore, diarrhea in the aged should ing, and most impor
AM. J. DIGEST. DIS. 18:9 (Sept.) 1951[5]
1. In a series of 37 pediatric patients with bowel dysfunction, including constipation, diarrhea, and irritable bowel syndrome, methylcellulose was a helpful adjunct to general management.
2. A good response was obtained in 34 of the cases and in most instances, it was possible to discontinue medication after a reasonable
N. Y. STATE J. MED. 52:1 (Jan.) 1952[4]
ries likewise responded to Cellothyl with a daily bowel movement of normal consistency. In three cases which required severe laxatives or periodic high enemas, there were established with Cellothyl daily evacuations nd stools. Although no improve-
PERMANENTE FOUND. M. BULL. 7:2 (July) 1949
A preliminary report is given on the therapeutic effectiveness of methylcellulose in the management of chronic constipation. The material was of beneficial effect in most patients suffering from rectal constipation and in a large number of patients suffering from constipation due to spasticity of the colon. Atony of the bowel apparently required more stimulation than
J. OKLAHOMA M. A. 43:360 (Aug.) 1950[7]
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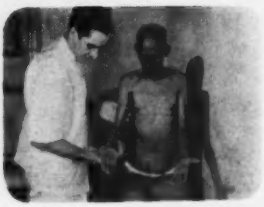

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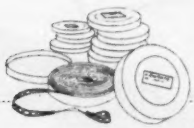

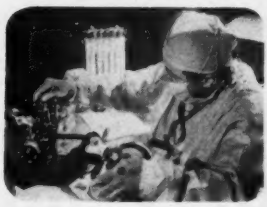

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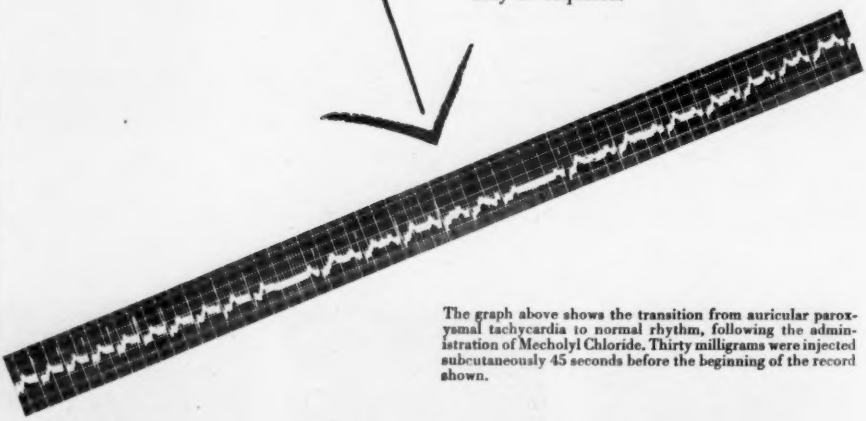

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CONTROL OF HYPERTENSION BY HEXAMETHONIUM AND 1-HYDRAZINOPHTHALAZINE

Preliminary Observations

HENRY A. SCHROEDER, M.D.
ST. LOUIS

SUCCESSFUL control at normotensive levels of the elevated blood pressure of human arterial hypertension theoretically should prevent or forestall all the secondary pathological changes resulting from increased arterial tension. There is, however, a wide body of opinion to the effect that hypertension, once established, is a disturbance necessary or "essential" for the maintenance of circulatory function. With this hypothesis I disagree. Sclerotic and narrowed coronary or cerebral arteries might become thrombosed when intra-arterial tension is lowered, especially if their respective arteriolar beds remain constricted; markedly inadequate renal blood flow may be lowered if renal blood vessels are sclerotic; but these conditions are not common to most cases of arterial hypertension.

A true antihypertensive drug of only moderate potency, 1-hydrazinophthalazine,[1] was found to be considerably more effective in treatment of patients who had had an unsuccessful sympathectomy than in those suffering from uncomplicated hypertension.[2] Malignant hypertension was also found to be susceptible to its action. This observation led to the hypothesis that "medical" sympathectomy induced by sympatholytic or ganglionic blocking agents might enhance the antihypertensive action of 1-hydrazinophthalazine. Because the latter drug apparently acts at various levels, on the brain (possibly the hypothalamus) and on peripheral arterioles, and has a wide spectrum of activity in antagonizing humoral pressor substances, i. e., hypertensin,[3] sustained prèssor principle,[3a] serotonin,[4] pherentasin,[3b] and arterenol (nor-epinephrine),[5] it was decided to combine its use with

Read before the Twenty-Fourth Annual Meeting of the Central Society for Clinical Research, Chicago, Nov. 2, 1951.

From the Hypertension Division, Department of Internal Medicine, Washington University School of Medicine, under a Grant-in-Aid from the National Heart Institute, United States Public Health Service.

1. Generous supplies of 1-hydrazinophthalazine were provided by Ciba Pharmaceutical Products, Inc., Summit, N. J., with the cooperation of Dr. F. H. Mohr, Dr. F. W. Yonkman, and Dr. C. H. Sullivan. The drug has been named "apresoline."

2. Schroeder, H. A.: The Effect of 1-Hydrazinophthalazine in Hypertension, Circulation **5**:28, 1952.

3. (*a*) Helmer, O. M.: Personal communication to the author. (*b*) Schroeder, H. A.: Personal observations.

4. Taylor, R. D.; Page, I. H., and Corcoran, A. C.: A Hormonal Neurogenic Vasopressor Mechanism, A. M. A. Arch. Int. Med. **88**:1 (July) 1951.

5. Freis, E. D., and Finnerty, F. A., Jr.: Suppression of Vasomotor Reflexes in Man Following 1-Hydrazinophthalazine (C-5968), Proc. Soc. Exper. Biol. & Med. **75**:23, 1950.

that of a soluble, apparently innocuous ganglionic blocking agent, hexamethonium chloride.[6] By this method two or more factors leading to the production of arterial hypertension, the neurogenic and some humoral ones, would be attacked. In addition, an evaluation of the importance of the neurogenic factor as a cause of hypertension might be made. The present report deals with the short-term results of combined therapy in 40 patients suffering from hypertension of all degrees of severity and offers a practical, if slightly cumbersome, method for control of elevated blood pressure at reasonable or normal levels. The long-term results will depend upon changes in eventual mortality rates. The method here discussed has been reported previously.[7]

METHODS

Patients were selected only in so far as they suffered from chronic arterial hypertension of enough severity for them to enter the hospital and of enough resistance to ordinary forms of therapy (dietary measures, thiocyanate administration, surgical measures, psychotherapeutic procedures) for their physicians to have prognostic doubts of halting the process. Most were studied in the private service of Barnes Hospital; a few were supervised in the wards. Diagnostic procedures included rough evaluation of renal function by tests of concentrating ability of the kidneys for urine and the rate of excretion of phenolsulfonphthalein injected intravenously; a rough evaluation of cardiac damage by electrocardiography and roentgenograms; an estimation of the lability of blood pressure by its fall during sleep induced by amobarbital (amytal®) sodium, and careful examination of the ocular fundi. Blood pressure was measured every four hours day and night with the patient in the recumbent position.

The usual procedure was to administer hexamethonium chloride in initial doses of 125 to 250 mg. every eight hours, increasing the dose daily until a maximum of 500 mg. every four hours was reached, or sustained hypertension had been converted into blood pressure showing wide fluctuations reaching normal levels. At this point 1-hydrazinophthalazine was added in doses of 25 to 50 mg. every eight hours, increasing the amount by daily increments until a dose of 100 mg. every four hours was reached or the blood pressure had become normotensive. The rate at which doses of both drugs were increased depended upon clinical evaluation of the hypertension and of its reaction to the drugs. In severe cases hexamethonium bromide was given parenterally in doses of 10 to 50 mg. every four or eight hours. Normotension (systolic pressure below 140 mm. Hg and diastolic pressure below 90 mm. Hg) was the aim in each case save those of older persons with severe arteriosclerosis. The blood pressure was taken before each dose, and the hexamethonium was omitted if systolic pressure was below 120 mm. Hg (or 130 to 140 mm. Hg in the older persons). As blood pressure fell to normal, the amount of hexamethonium thus was automatically adjusted; if wide swings occurred, part of the dose was omitted at chosen levels (for example, the full dose was given if the systolic pressure was more than 140 mm.; half the dose, if 130 to 140; one-fourth the dose, if 120 to 130, and none, if below 120). Determination of the presence and degree of postural hypotension was made frequently.

After normotension had been achieved in the hospital and maintained for a week or longer, a member of the patient's family was instructed in the method of measuring blood pressure and the necessary apparatus was purchased. The amounts of the drugs were reduced by omitting one night dose; a schedule was arranged for use at home, and the patient was discharged from the hospital.

Generally the symptoms of hypotension had been experienced one or more times by the patient; these were explained as signals to omit a dose of hexamethonium if the blood-pressure

---

6. Adequate supplies of hexamethonium chloride were provided by Chilcott Laboratories, Division of the Maltine Company, Morris Plains, N. J., through the courtesy of Dr. W. T. Strauss.

7. Schroeder, H. A.: Effects of Hexamethonium Chloride and 1-Hydrazinophthalazine in Hypertension, J. Lab. & Clin. Med. **38**:949, 1951; Inactivation of Pressor Substances in Hypertension, read before the Second International Gerontological Congress, St. Louis, Sept. 9, 1951; Newer Drugs in the Treatment of Hypertension, read before the New England Postgraduate Assembly, Boston, Nov. 9, 1951.

reading could not be taken. At home it was determined before each dose when convenient for the patient; in the case of those working full time it was measured in the morning, on return from work, and twice in the evening. Doses of hexamethonium were adjusted to the levels of systolic pressure. Records of blood pressure and amount of drug taken were maintained by each patient. In the case of persons of lower economic and intellectual status, this method could not be used for obvious reasons; they were seen at weekly intervals in a special clinic and their condition evaluated. Teaching groups were established for both types of patients in which the actions of the drugs and the methods for control of hypertension were discussed. The maximal doses given in the severest cases totaled 6.0 gm. of hexamethonium chloride and 900 mg. of 1-hydrazinophthalazine per day; the smallest effective dose was 375 and 75 mg., respectively. As no "standard" dose could be determined in advance the effective doses varied from time to time; the amount was adjusted carefully to the needs of each patient. The average amount for control of benign hypertension was approximately 2.5 gm. of hexamethonium and 500 mg. of 1-hydrazinophthalazine. Patients with severe renal insufficiency were not included in this series.

RESULTS

In every case blood pressure was lowered markedly and maintained temporarily at lower levels by the use of hexamethonium and 1-hydrazinophthalazine.

TABLE 1.—*Control of "Benign" Arterial Hypertension with Hydrazinophthalazine and Hexamethonium*

Approximate Average Level of Control Pressure, Mm. Hg *	Number of Cases	Average Blood Pressure * Maintained at				Duration, Wk.
		160/100 Mm. Hg	150/90 Mm. Hg	140/90 Mm. Hg	130/80 Mm. Hg	
250/150	1	..	..	1 †	..	14
230/140	3	1 †	2	..	..	17-20
210/130	9	3 †	..	3	3 ‡	4-25
200/120	8	2 ‡	3 §	2	1	4-21
180/110	3	..	..	3	..	19-30
170/100	1	..	1	..	..	23
Totals	25	6	6	9	4	

* Systolic/diastolic.
† Unsuccessful sympathectomy.
‡ Two patients discontinued treatment.
§ One patient discontinued treatment.

Benign Arterial Hypertension.—In the hospital 14 of 20 patients with benign arterial hypertension achieved sustained average normotensive levels of 140 mm. Hg systolic and 90 mm. diastolic or below in the supine position. Blood pressures in four arteriosclerotic persons were deliberately not reduced to this point, and two were discharged with systolic levels of 150 to 160 mm. At home these levels were usually not sustained because of the appearance of intermittent hypotensive symptoms; therefore, the dose was reduced and the systolic pressure maintained between 130 and 160 mm. Hg. The results are indicated in Table 1, and examples are shown in Figures 1 to 4.

Malignant Hypertension Without Renal Insufficiency.—Only 4 of 15 patients in the malignant stage of hypertension achieved and maintained strictly normotensive levels with oral administration of the preparations. In all but two, blood pressure was reduced to approximately 160 mm. systolic and 100 mm. diastolic for a week or more with oral and parenteral administration of hexamethonium, not sustained at home. The malignant state reversed itself in 13 and had not recurred

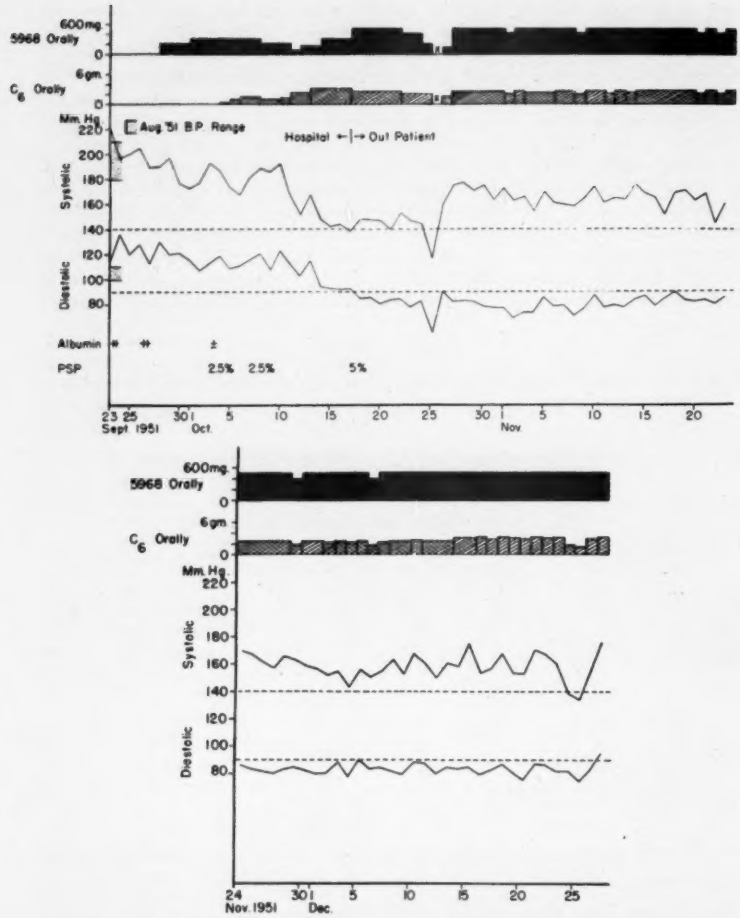

Fig. 1.—C. E. was a 51-year-old man who had had renal hypertension for one and a half years, the range of which is shown in the shaded area. His blood pressure had gradually risen to its present level during the year and a half before admission. Albuminuria accompanied the onset of hypertension, and it was possible that he suffered from glomerulonephritis. The administration of 1-hydrazinophthalazine (5968) was accompanied with severe prostration and headaches, with only slight effect on the level of blood pressure. The addition of hexamethonium (C6) therapy produced the desired results. Note the low excretion of phenolsulfonphthalein (P. S. P.), 2.5% in 15 minutes, which was not altered during the normotensive period. At the top of the chart the "X" indicates two days in which he had food poisoning and marked hypotension, with one reading as low as 90/60. He remained symptom-free and working. His blood pressure was allowed to rise slightly because periods of postural hypotension appeared which made it difficult for him to carry on full activities.

In this figure and following ones *5968* represents 1-hydrazinophthalazine; *C6 parenterally* represents hexamethonium bromide, and *C6 orally* represents hexamethonium chloride. Shaded area in beginning of chart shows extremes of blood pressure during control period. *P. S. P.* represents excretion of intravenously injected phenolsulfonphthalein in 15 minutes. Each blood-pressure point represents the daily average of six readings when the patient was in the hospital and of five when he was an outpatient, taken at four-hour intervals. All measurements were made in the supine position.

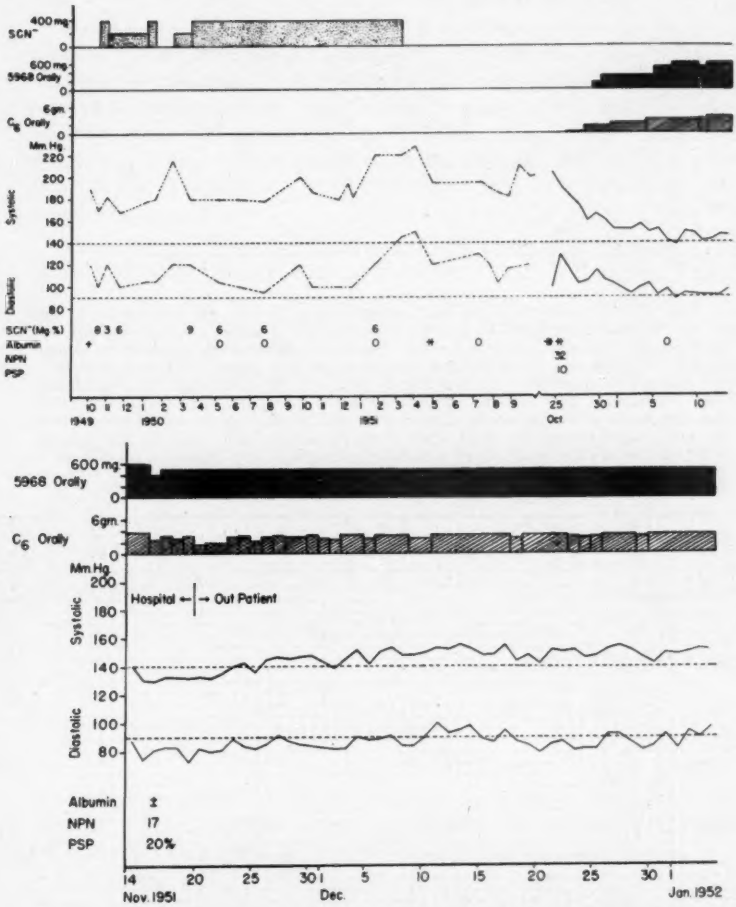

Fig. 2.—Effect of hydrazinophthalazine and hexamethonium therapy in neurogenic hypertension. D. B. was a 56-year-old woman who had had moderate to marked hypertension for seven years. Although she had many symptoms, dyspnea on exertion and at night was her major complaint, requiring digitalis treatment for relief. Two courses of therapy with potassium thiocyanate (*SCN*) were without marked effect upon the level of blood pressure. It was believed that her condition was deteriorating. Nonprotein nitrogen in her blood was above the upper limit of normal, and she was able to excrete only 10% of injected phenolsulfonphthalein in 15 minutes. Control of her blood pressure at normotensive levels resulted in virtual disappearance of albuminuria, a fall in nonprotein nitrogen to normal, and an increase in the excretion of phenolsulfonphthalein. She has remained well, with the exception of serous otitis media. Severe headaches were completely relieved. Notations are explained in legend to Figure 1.

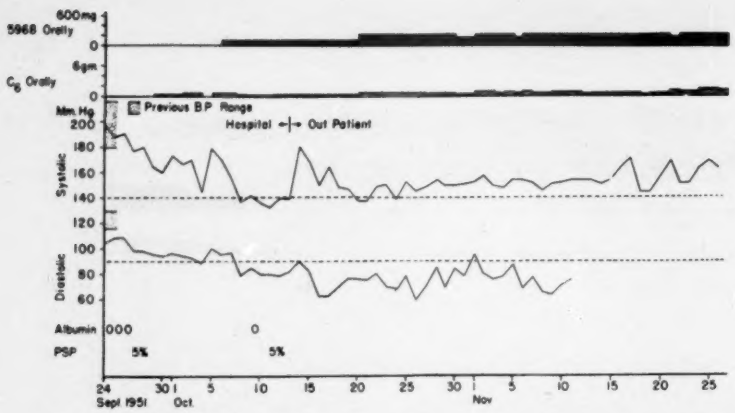

Fig. 3.—Effect of hydrazinophthalazine and hexamethonium therapy in arteriosclerosis and hypertension. B. H. was a 69-year-old woman who had severe general arteriosclerosis and moderate hypertension responding well to control. She had suffered from transient hemiplegia before admission. While it was felt that normotension might precipitate coronary occlusion, it did not. She remained symptom-free and was able to carry on her usual activities. Resumption of activity was accompanied with increase in the level of blood pressure, which was deliberately not controlled because of occasional spells of weakness. All blood-pressure measurements were made by the same nurse except for those after Nov. 10, which were taken by the patient's husband. Note the relatively small doses necessary. Notations are explained in legend to Figure 1.

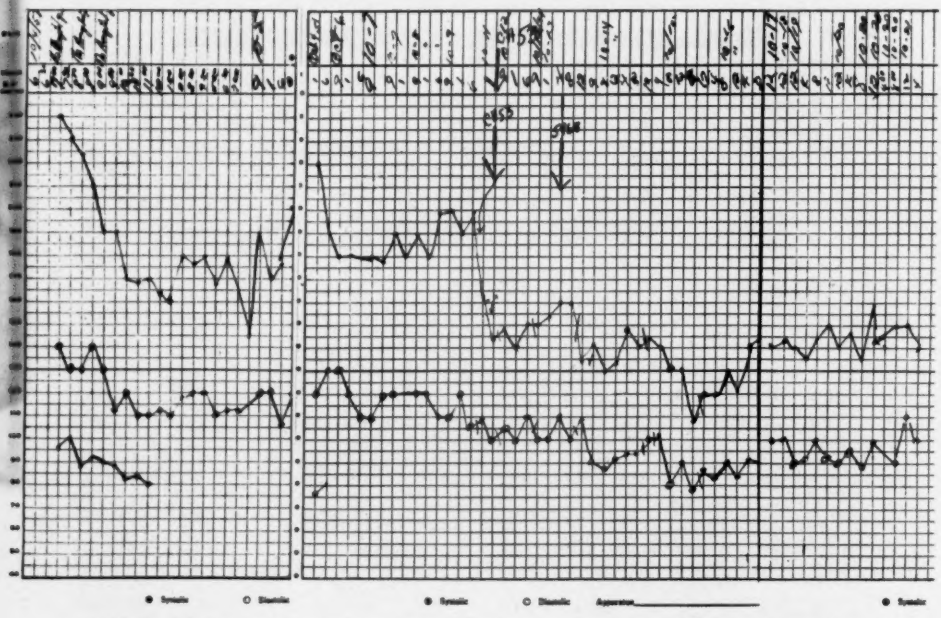

Fig. 4.—Blood-pressure readings as recorded daily on patient's chart. Patient R. P. was a 47-year-old man suffering from severe neurogenic hypertension. At left is shown response of his blood pressure to sleep induced by amobarbital sodium, measurements being made hourly throughout the night. At right at arrow marked "CH_m" is shown effect of hexamethonium chloride given orally in doses increasing from 1.5 to 3.0 gm. per day. Second arrow, marked "5968," indicates effect of 1-hydrazinophthalazine added to hexamethonium. Because of the hypotension induced, dose of hexamethonium was reduced to 2 gm. per day. During first few days of normotension, the patient complained of weakness, which disappeared quickly. He has remained relatively normotensive.

at the time of writing. Three were relieved of left ventricular failure (Table 2; Figs. 5 to 8).

Unsuccessful Sympathectomy.—The supine blood pressure of patients who had previously been subjected to lumbodorsal sympathectomy was more difficult to control at normotensive levels than that of those who had not, because of the development of severe postural hypotension. In fact, it was generally necessary to maintain moderately hypertensive levels in the supine position (160 to 170 mm. systolic) in order to avoid symptoms in the standing position. A postural fall of 20 to 30 mm. was often converted into one of 50 to 70 mm. with the use of these agents (Table 1; Fig. 9).

Side-Actions.—1-Hydrazinophthalazine acts as an antihistaminase.[8] Therefore, patients suffering from hypertensive headaches, most of which are probably histaminic in origin, may have them induced by this drug.[2] Although headaches eventually disappear as use of the drug is continued, the prostration, nausea, and vomiting

TABLE 2.—*Effect of Hydrazinophthalazine and Hexamethonium Therapy on "Malignant" Stage of Hypertension*

Approximate Average Level of Control Pressure, Mm. Hg *	Number of Cases	Average Blood Pressure * Maintained at				Duration, Wk.	Comment
		200/130 Mm. Hg	170/110 Mm. Hg	160/100 Mm. Hg	140/90 Mm. Hg		
300/200	1	..	..	1 †	..	4	Acute malignant stage
260/170	5	2 ‡	1	2	..	2-16	3 not controlled by preparation given orally; 1 died
240/150	4	..	2	2	..	14-23	1 not controlled by preparation given orally
220/140	3	..	..	3	..	8-20	1 with heart failure died of pneumonia
200/130	2	..	..	..	2	16-25	1 with heart failure
Totals	15	2	3	8	2		

* Systolic/diastolic.
† Discontinued treatment.
‡ Two patients discontinued treatment.

which may accompany its administration can be serious complications for several days. The prior administration of hexamethonium abolished or prevented this action of 1-hydrazinophthalazine in subjects susceptible to headaches.

Hexamethonium chloride paralyzes both adrenergic and cholinergic nerve impulses at the autonomic ganglia. Its side-actions, therefore, include all the signs of autonomic paralysis. Fortunately the doses used in most cases of hypertension were small enough that serious side-actions were not encountered. Constipation was seen in almost every case, readily controlled by administration of cascara sagrada fluid extract or milk of magnesia (magnesia magma) or when severe, by treatment with bethanechol (urecholine®) chloride. Other reactions included blurring of vision in hyperopic persons, sluggish reaction of the pupil to light with photophobia, dryness of the mouth, minor digestive disturbances, retention of urine in the bladder, diminished sweating, warm dry hands and feet, and disturbances of the regulation of body temperature on hot or cold days. These effects of hexamethonium were of minor degree with usual doses and tended to disappear as

8. Meier, R., and others: Personal communication to the author.

administration of the drug was continued. With the larger doses necessary in treatment of the malignant stage of hypertension, temporary paralysis of the bowel was observed twice, attacks of diarrhea were encountered in three cases, constipation was severer, and blurring of vision was more annoying to far-sighted persons. No cumulative toxic effects have been observed in patients taking 1-hydrazinophthalazine alone for a year or more.

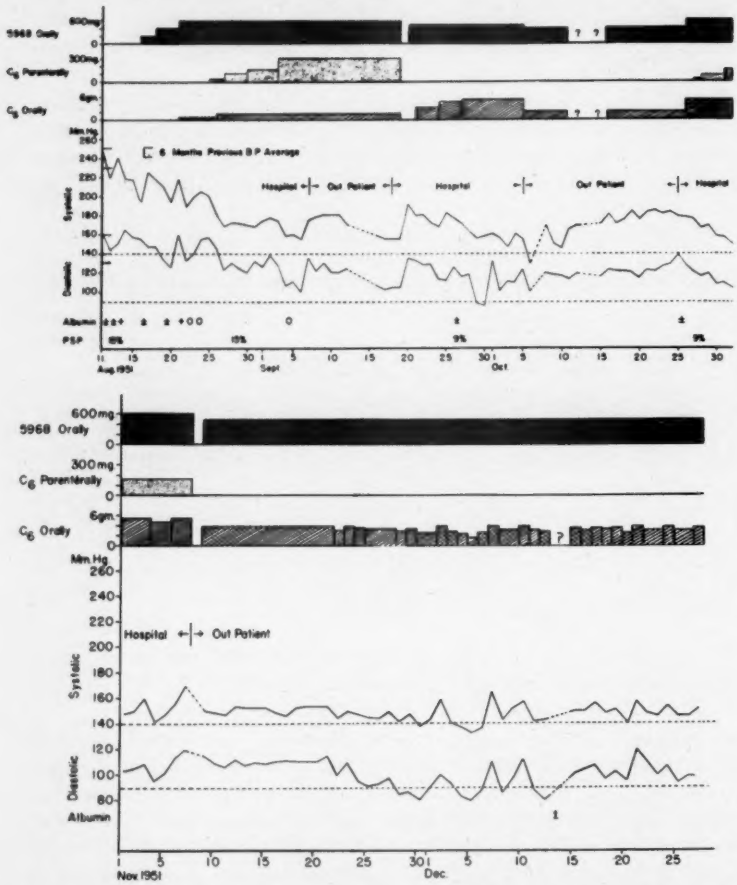

Fig. 5.—Effect of hydrazinophthalazine and hexamethonium therapy on course of malignant hypertension. D. L., a 37-year-old man, suffered from severe hypertension in the malignant phase without renal insufficiency. His ocular fundi showed Grade IV changes. Hydrazinophthalazine therapy appeared to cause a slight alteration in the level of blood pressure; addition of hexamethonium given orally and parenterally apparently caused further control, which was partly continued at home. Omission of one day's medication resulted in a rise which was counteracted in two weeks' time in hospital. At the blank space on Oct. 10, he omitted or took the drugs sporadically because he became tired of the regimen. On his third admission control was more easily accomplished. The ocular fundal changes reverted rapidly to Grade I, and he was symptom-free; side-actions of drugs disappeared. Blood pressure has been maintained at reasonable but not normal levels while at home. Notations are explained in legend to Figure 1.

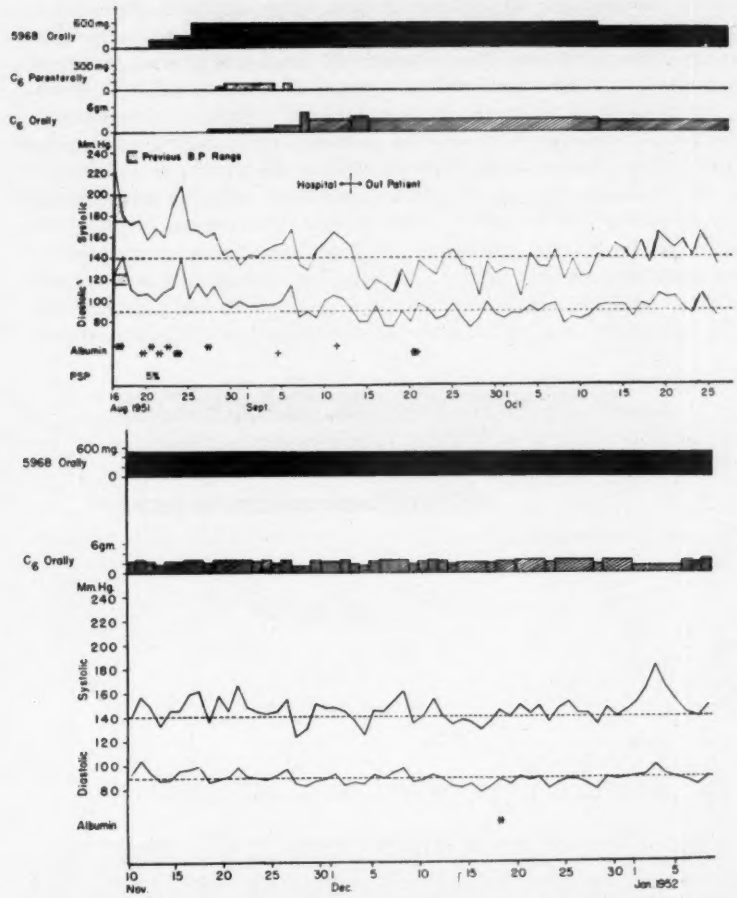

Fig. 6.—Effect of hydrazinophthalazine and hexamethonium therapy in hypertensive heart failure. I. M. was a 47-year-old Negro woman suffering from severe hypertension for three years, intermittent left ventricular insufficiency for two years, and the malignant stage for four months. Her ocular fundi revealed Grade IV changes; there was severe paroxysmal nocturnal dyspnea, because of which she had been forced to sleep in a chair; right pleural effusion was present. Because of symptoms, the drugs were given shortly after admission. Her blood pressure has remained at relatively normal levels. All signs of left ventricular failure have disappeared, although digitalis administration was discontinued in the hospital, and she was able to return to work. Albuminuria diminished in the hospital but returned after discharge. Her ocular fundi reverted to normal, except for the presence of many white scars. During the second week in October a slight reduction in the dose was accompanied with a slight elevation of blood pressure. Her records for early November were destroyed, but at no time did her systolic pressure reach 160 mm. Hg on any one determination; it generally remained between 120 and 150 mm. She remained completely free of symptoms or side-effects of the drugs. On Jan. 1 she voluntarily decreased the dose of hexamethonium to one-half the usual amount. Her average blood pressure rose rapidly, a single determination being as high as 190/104. Resumption of the usual dose was followed by a return to normotensive levels. For the first time in three years she has been able to work a full eight-hour day in a restaurant. Notations are explained in legend to Figure 1.

Tolerance.—No instances of tolerance to these agents appeared after normotension had become established. In fact, patients tended to use less hexamethonium after a month or two of normal blood pressure. In every case in which escape of the blood pressure to uncontrolled levels was suspected, it was found to be due to omission of regular doses or to irregularity in taking the drugs. In the malignant stage, in which normotensive levels were not sustained, experiences differed. Two persons appeared to develop partial tolerance while in the hospital (Fig. 8); after discharge their courses were only moderately satisfactory, although the malignant state was altered into one apparently more benign. One person, in whom the results were definite but not satisfactory, displayed considerably lower levels of arterial tension during the two months after discharge; she had refused to remain in the hospital until adequate therapy had been given. One young woman who entered the hospital in deep coma caused by hypertensive encephalopathy reacted

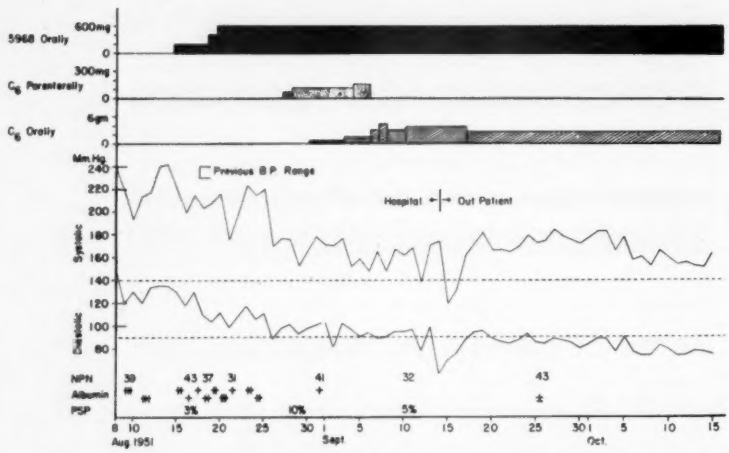

Fig. 7.—Effect of hydrazinophthalazine and hexamethonium therapy in congestive failure. A. K. was a 55-year-old man in the malignant stage of hypertension with left ventricular failure. There were pleural effusion, enlargement of the liver, elevated venous pressure, and paroxysmal nocturnal dyspnea and orthopnea. His blood pressure fell to moderately elevated levels and remained there, the diastolic pressure being normal. Signs of heart failure disappeared, and the cardiac shadow, as determined by roentgenograms, regressed considerably in size. Digitalis administration was discontinued while he was in the hospital. He became somewhat underactive and apathetic mentally but was otherwise symptom-free. The ocular fundal changes reverted from Grade IV to Grade O, and an abnormal electrocardiogram became normal. The dose of hexamethonium was decreased because of the appearance of hypotension at home. On Oct. 17 he had acute lobar pneumonia which was rapidly progressive, and he died on Oct. 19. Note lack of change in nonprotein nitrogen in the blood and the decrease in albuminuria at lower levels of blood pressure. Notations are explained in legend to Figure 1.

rapidly and favorably to the drugs for three weeks; tolerance then appeared which was not reversed by parenteral therapy, and she died of cardiac failure two weeks later. One older woman in the late stages of severe malignant hypertension became partially resistant. The remainder of the patients suffering from malignant hypertension appeared to become more susceptible to the actions of the drugs during two to three months' observation.

Secondary Pathological Changes.—In every case of malignant hypertension, papilledema and retinal hemorrhages disappeared rapidly, the latter often being absorbed in as little as a week. Exudative lesions regressed more slowly, and scars were observed to persist in ocular fundi for five months or more. Reversal of fundal changes from Grade IV to Grade I (according to classification of Keith and Wagener) or to normal was observed in five of nine patients and from Grade III to Grade I or less in all of five. Visual disturbances caused by retinal lesions were present in seven patients; slow recovery of vision occurred in all, but four to five months later four continued to complain of residua. Coma resulting from hypertensive encephalopathy was completely abolished in one young woman in less than 12 hours, and early encephalopathy was relieved rapidly in five others.

Whenever albuminuria was present, it diminished or disappeared; in one case it returned later. Renal function, as measured by the rough tests at my disposal,

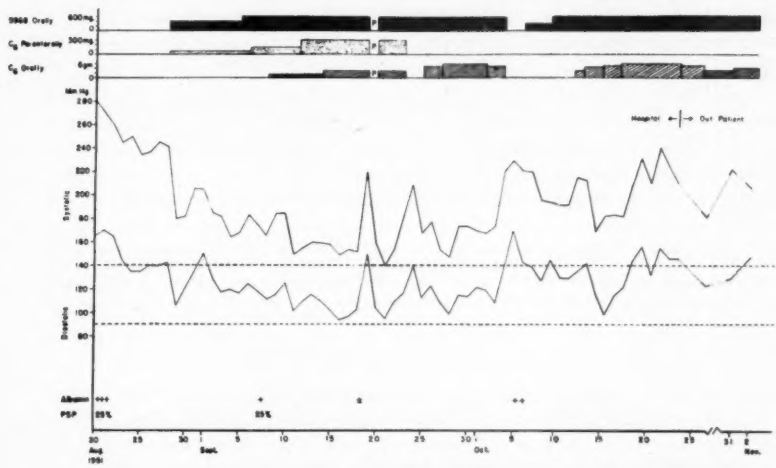

Fig. 8.—Failure of oral therapy with hydrazinophthalazine and hexamethonium in severe malignant hypertension. B. B. was a 28-year-old Negro woman with severe malignant hypertension and hypertensive encephalopathy and in semicoma. Hydrazinophthalazine was given intravenously shortly after her admission in an attempt to abort a convulsion, which resulted in regression of symptoms and a considerable fall in blood pressure (not shown on chart). Her blood pressure fell to relatively normotensive levels while hexamethonium bromide and hydrazinophthalazine were being given parenterally. At "P" placebos, administered for one day, resulted in a rapid rise of blood pressure reaching a level of 290/190 (not shown in the average reading on the chart). The reinstitution of the drug administration was followed by a fall, but when hexamethonium treatment was stopped the blood pressure again rose, only to fall temporarily on oral administration of hydrazinophthalazine and hexamethonium. Cessation of the drug therapy again was followed by a rise of blood pressure. It was not controlled by oral administration of the preparations, although the malignant stage was reversed, as determined by regression of ocular fundal changes. The patient discontinued the medication herself and refused to return for follow-up study. She died Nov. 16 of a cerebral hemorrhage. The large doses of hexamethonium caused severe constipation and blurring of vision, partly controlled by bethanechol chloride treatment. Note the lack of change in renal function and the diminution of albuminuria at lower levels of blood pressure. Notations are explained in legend to Figure 1.

was not significantly depressed at lower levels of blood pressure in any case but one discussed below; in 10 it increased slightly. Abnormal microscopic elements in the urine disappeared or diminished in all; in one, gross hematuria was completely

relieved. A noteworthy change was a fall in the level of nonprotein nitrogenous material in the blood to very low values, observed in six instances.

Congestive heart failure characterized by dyspnea, pulmonary congestion, and orthopnea was completely relieved in all of three instances; digitalis administration was discontinued without adverse effect. Roentgenograms showed that the heart became smaller in only six cases. Electrocardiograms reverted from changes characteristic of left ventricular strain in 11 instances; in 5 the records became normal. A summary of the results is shown in Table 3.

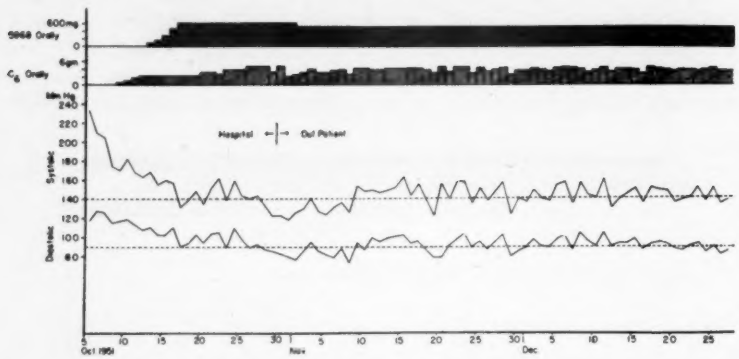

Fig. 9.—Effect of hydrazinophthalazine and hexamethonium therapy in combined neurogenic and renal hypertension. A. R. was a 34-year-old woman who had suffered from recurrent attacks of right pyelonephritis since the birth of her child 15 years previously. She had had severe hypertension one and a half years and had refused sympathectomy. Her renal function was within normal limits, and there was no albuminuria. Control of hypertension resulted in disappearance of headache, tinnitus, palpitation, anxiety, and nervousness. She has remained completely free of symptoms. Notations are explained in legend to Figure 1.

TABLE 3.—*Summary of Findings in Forty Cases*

	Number of Cases	
Malignant Hypertension Without Nitrogen Retention		15
Ocular fundi Grade IV	11 *	
Regressed to Grade III	4	
Regressed to Grade I or II	5	
Ocular fundi Grade III, regressed to Grade I or II	5	
Renal function reduced	0	
Malignant stage reversed temporarily	13	
Congestive failure present and relieved	2	
Tolerance to drug developed	2	
Use of drugs voluntarily discontinued	4 †	
Malignant Hypertension with Nitrogen Retention		4 ‡
Renal function reduced	3	
Course altered	0	
Benign Hypertension		20
Renal function reduced	0	
Tolerance to drugs developed	0	
Use of drugs voluntarily discontinued	3 †	
Unsuccessful Sympathectomy		5
Normotensive levels achieved at home	0	
Renal function reduced	0	
Tolerance to drugs developed	0	
Use of drugs voluntarily discontinued	0	
		44

* One died.

† Use of drugs was discontinued for the following reasons: lack of cooperation and low-grade intelligence, 5; impotence, 1; other side-actions, 1.

‡ Not included in this series of 40 cases but shown to indicate limits of therapy in renal insufficiency.

Subjective Changes.—Unmeasurable subjective symptoms accompanying hypertension which disappeared, when present, after lower blood pressures had become established included headaches, palpitation (relieved in all but one), tinnitus (relieved in the only one complaining of it), exertional dyspnea, and emotional sweating (of axillae and extremities). Excess emotional drive, nervous tension, and anxiety were said to have diminished in all but two patients; businessmen in highly competitive pursuits generally complained of lessened activity, although others welcomed the feeling of relaxation associated with normotension. Many patients stated that they had not felt as well in several years. Three had complaints suggestive of, and accompanied with, hypotension until doses were readjusted. One noticed no change in emotional tension, and two complained of intermittently increased nervous tension associated with hypotension.

Theoretical Complications of Normotension.—Obviously, a lowered arterial tension may theoretically lead to ischemia of an organ if a large artery is narrowed by arteriosclerotic changes and the arteriolar bed does not dilate, or if the arteriolar bed is severely constricted by disease. The brain, heart, and kidney are considered to be the most vulnerable in this respect. Cerebral ischemia and coronary and renal insufficiency may be induced by lowering the arterial tension, unless this lowering is accompanied with vasodilatation distal to the narrowed artery or in the peripheral bed. Signs which might be interpreted as cerebral ischemia (drowsiness, apathy, coma) were encountered in five instances, but in only one was semicoma produced; these disappeared in one or two days. There was no evidence in any case of cerebral arterial thrombosis, a possible complication. Angina pectoris occurred once in one case and twice in a second, caused apparently by the 1-hydrazinophthalazine; it was relieved in another case in which blood pressure was lowered. Coronary occlusion did not occur but remains a possible complication when sclerosis of the coronary arteries is advanced.

In one case, that of a 28-year-old Negro woman, renal insufficiency was induced by too rapid lowering of blood pressure. The patient suffered from severe malignant hypertension, with encephalopathy and retention of nitrogen in her blood. Small doses of the two drugs were given simultaneously in an effort to abort convulsions; her systolic blood pressure fell in a few hours from very high levels to approximately 110 mm. Hg and her diastolic pressure to 70 mm., where they remained for four days. Anuria accompanied the hypotension for two days only; escape of the blood pressure from therapeutic control to previous high levels precipitated pulmonary edema, from which she died. At autopsy multiple small, diffuse, fresh myocardial infarctions were observed. Obviously the rapid fall of blood pressure was detrimental to blood flow in myocardium and kidney. In no other case was such an incident observed, although it was constantly considered. Slow, progressive control of hypertension apparently prevented such acute ischemic complications.

Reactions Accompanying Normotension.—When normotension was finally established, most patients complained of lassitude, weakness, and lethargy for one to three days. After this period, energy returned and strength was regained. Readjustment of unknown mechanisms apparently was responsible, for if hypertension was allowed to recur a similar period was again experienced after the reinduction of normotension. No observable chemical or physiological alterations were detected which might account for this phenomenon.

The pulse rate was usually normal or lower than normal; body temperature obtained by rectum tended to be low. Postural hypotension was detectable at first but seldom amounted to more than 20 to 30 mm. Hg systolic; it regressed or disappeared after several weeks. Severe emotional stimuli were found to result in moderate "spikes" of transient hypertension which could be directly attributed to the stimuli; their complete control in persons frequently subject to them was found to be impossible, owing to the severe hypotension developing when the patient was undisturbed. Hypotensive episodes induced by the drugs were often followed by transient hypertensive "overshoots."

Failures.—Complete failure temporarily to lower blood pressure significantly was not encountered in this series as long as use of the drugs was continued. Omission of a single dose or several doses always was followed by elevation of blood pressure; the administration of placebos rapidly induced the same result. Four persons with malignant hypertension and three with the benign type omitted or neglected to continue taking the drugs through carelessness or lack of understanding; hypertension recurred in all, reaching the levels sustained before treatment. Three were recontrolled; two continued sporadic self-administration, and two gave up the medication with serious results. It was conservatively estimated that life was prolonged in six instances; two failures in the severest type of case were discussed above.

Limits of Regimen.—The regimen used in these cases was found to have the following limits of effectiveness: (*a*) Malignant hypertension was usually only partially controlled; two failures were observed. The severer it was, the less amenable it was to therapy. (*b*) Although nitrogen retention was abolished when of minor degree, it was unaffected when of marked degree. (*c*) Severe arteriosclerosis of the coronary arteries in older persons led to angina pectoris in two patients; both had experienced similar attacks previously. (*d*) Lack of intelligent management by the patient himself led to failure; the more intelligent the patient was, the more able he was to maintain adequately satisfactory levels of blood pressure at home. (*e*) Hospitalization for two to four weeks was required in order to observe the changes constantly; successful induction of the normotensive state in ambulatory patients was achieved in only two-thirds of those in whom it was attempted because of the period of weakness and lassitude accompanying its induction, which led to omission of the medication.

Reaction of Patient to Regimen.—Most patients were willing to undergo the constant self-supervision of blood-pressure levels and the self-administration of drugs in order to obtain the physical relief from symptoms and the emotional relief from fear of consequences of hypertension. Only one showed extreme nervousness at the prospect of blood-pressure measurements. Intelligent patients in the higher economic brackets were able to adjust themselves to the regimen with relative ease; most had been severely restricted in their activities by their physicians and welcomed the loss of restrictions other than medication. Those of outpatient clinic and ward status performed less satisfactorily, the attrition due to inattention being roughly 25%. Few complained of the burden imposed by the regimen, especially when interest was stimulated by classroom teaching.

Duration of Action.—Hexamethonium chloride acts rather rapidly, in one-half to one hour after oral ingestion, and is effective four to eight hours. It appears to be partly excreted in the urine and partly metabolized. 1-Hydrazinophthalazine appears to exhibit a similar duration of action when taken by mouth and a similar fate.[9] After intravenous injection, its full effect appears slowly in one-half hour and lasts four to six hours. Renal insufficiency was, therefore, accompanied with potentiation of the actions of both drugs. When patients inadvertently omitted a dose, or a placebo was substituted, the blood pressure four hours later was usually elevated moderately, although full escape did not occur for 12 to 15 hours. Patients quickly learned the necessity of frequent doses by experiment on themselves in which doses were omitted.

COMMENT

The results here reported can be evaluated only from the short-term viewpoint. They are striking in benign hypertension, less so in malignant hypertension, and unsatisfactory in the severest cases. Only time will tell whether chronic toxic manifestations will develop, tolerance or increased susceptibility will appear, the underlying tendency to hypertension will be altered favorably or unfavorably, and the fatal consequences of hypertension can be avoided.

These drugs act on the hypertensive process at two general areas. Presumably hexamethonium inhibits neurogenic vasoconstriction, which includes the renal vascular bed, at the ganglionic level.[10] Its failure to act alone in a satisfactory manner, although it induces wide fluctuations of blood pressure, suggests that other pressor mechanisms are operating. Among these may be the renal pressor mechanism of acute renal ischemia mediated through renin and its effector substance, hypertensin, and the more slowly acting pressor mechanism, presumably renal in origin, whose effector substance is pherentasin. Pherentasin is the only pressor substance consistently found in hypertensive blood which is absent in normotensive blood.[11] 1-Hydrazinophthalazine abolishes the pressor action of both pherentasin and hypertensin, thereby possibly inhibiting a humoral pressor mechanism present in chronic hypertension. It is not surprising, therefore, that synergism exists with these two drugs. 1-Hydrazinophthalazine also appears to act upon an area of the

9. Experiments performed in this laboratory by Dr. H. Mitchell Perry have indicated that only approximately 5% of a compound similar to 1-hydrazinophthalazine has been recovered in the urine of patients taking this drug orally. The largest amount appears in the specimen voided 90 to 180 minutes after ingestion. (Perry, H. M.: A Method of Measuring 1-Hydrazinophthalazine in Body Fluids, Federation Proc., to be published). It is probable that the drug is altered in the body either during its reaction with pressor substances or by metabolic processes.

10. Hexamethonium ion has recently been shown to cause acute renal vasodilatation in normal dogs and man, while in hypertensive subjects with diseased kidneys the effects were much less pronounced (Mills, L. C.; Moyer, J. H., and Handley, C. A.: The Effect of Hexamethonium (C6) on Renal Hemodynamics: Laboratory and Clinical Evaluation, read before the American Federation for Clinical Research, Southern Section, Atlanta, Jan. 18, 1952). Apparently the action is directly contrary to that of arterenol (nor-epinephrine) (Mills, L. C.; Skelton, J., and Moyer, J. H.: Norepinephrine: The Effect on Renal Hemodynamics, read before the American Federation for Clinical Research, Southern Section, Atlanta, Jan. 18, 1952).

11. Schroeder, H. A., and Olsen, N. S.: Pressor Substances in Arterial Hypertension: II. Demonstration of Pherentasin, a Vasoactive Material Procured from Blood, J. Exper. Med. **92**:545, 1950.

brain, either at medullary levels or at the hypothalamus.[12] The mechanism is little understood. It is one of the rare truly antihypertensive agents known, increasing peripheral and renal blood flow while lowering blood pressure. In the experimental animal it does not resemble usual vasodilators in that once its effect is reached further injections do not produce further lowering of blood pressure. The action is slow to appear. Apparently some basic circulatory mechanism overactive in hypertension is inhibited by this substance.

The combined effects of these two drugs appear to be adequate, in the short term, for controlling the elevated blood pressure in most cases of benign arterial hypertension. The increment above normotensive levels which is not controlled in the malignant stage probably constitutes a third mechanism of undetermined nature that must be inhibited before complete reversal is possible. Experiences with thiol antipressor substances,[13] which are impractical for continuous therapy, suggest that they may exhibit a wider range of activity in the malignant state than the two drugs here reported on and supplement them effectively for only very brief periods.

No patient has been subjected to control of blood pressure merely because of asymptomatic hypertension. The treatment of abnormal "numbers" in an otherwise well person is unjustified at the present. Until the prevention of the effects of hypertension has been established by long-term observation, I do not believe that the regimen should be instituted in those exhibiting slightly or moderately elevated blood pressures without suggestive evidence of the imminence of cardiovascular or renal damage.

These are powerful drugs. Great caution must be exercised in administering them to patients with cardiovascular disease. Slow reduction in blood pressure is essential to prevent serious complications, as I have discovered.[14] The blood pressure, once controlled, must not be allowed to escape to hypertensive levels by omission of medication, as slow recontrol then becomes necessary, a prolonged process. Understanding of both circulatory hemodynamics and pharmacology is a prerequisite for any physician using the drugs in human beings.

Freis and associates [15] have recently reported on the effects of hexamethonium bromide given by injection every 12 hours to hypertensive patients, with alternating oral doses of 1-hydrazinophthalazine midway between each injection. The schedule of dosage used was such that elimination of one or the other drug must have

12. Gross, F.; Druey, J., and Meier, R.: A New Group of Depressor Substances with a Special Type of Effect, Experientia **6**:19, 1950.

13. Schroeder, H. A.: The Anti-Hypertensive Influence of Certain Sulfhydryl Compounds, Science **114**:441, 1951.

14. Two patients under the care of other physicians have died. The death of one was directly attributable to the drug therapy; blood pressure was lowered too rapidly, and sustained hypotension followed which was not overcome by administration of vasopressor drugs. The patient died of uremia. The other died suddenly one hour after both drugs were first given. Permissions for autopsies were not obtained. These two fatalities, and the one reported herein, stress the absolute necessity of careful supervision and slow reduction of blood pressure. In no circumstances do I initiate therapy with administration of the drugs together. Sensitivity to small doses of each has been observed, especially when renal insufficiency is present. When hemodynamics are altered with powerful agents in a cardiovascular disorder, utmost caution is essential to prevent accidents.

15. Freis, E. D.; Finnerty, F. A., Jr.; Schnaper, H. W., and Johnson, R. L.: The Treatment of Hypertension with Hexamethonium, Circulation **5**:20, 1952.

occurred during each 12-hour interval. Most of their results were not comparable with those here reported, probably for this reason. Several attempts to control severe hypertension completely by giving both drugs together on a six-hour schedule were only partly successful; control was achieved only on a four-hour schedule. Severe malignant hypertension with encephalopathy was controlled by hourly doses of hexamethonium bromide. The rapid renal elimination of this substance by good kidneys and the slow elimination by poor ones must be considered in therapy. The results are equally disappointing when both drugs are given every four hours during the day only, with a 12-hour rest at night.

It is always unfortunate when a new therapeutic method focuses attention of clinical investigators upon therapy and away from basic mechanisms. Research leading to understanding is thus effectively stifled. In the case of the present report, more questions are raised than are answered. It is obvious that a neurogenic autonomic factor is of considerable importance in pathogenesis; equally obvious that another, probably humoral, factor is of similar importance, for neither drug acts effectively alone. The existence of a third factor in malignant hypertension, possibly also humoral, is based upon the lessened effectiveness of both drugs in this state. Research on basic causes must continue at an accelerated rate for the condition to be fully controlled or prevented.

SUMMARY AND CONCLUSIONS

Hexamethonium chloride and 1-hydrazinophthalazine were given by mouth to 40 patients suffering from arterial hypertension of all degrees of severity for periods of 4 to 25 weeks, in hospital and then at home.

"Benign" arterial hypertension was effectively controlled at normotensive or nearly normotensive levels in every case. Continuous administration was essential for control. Slight postural hypertension resulting from unsuccessful sympathectomy was markedly enhanced.

"Malignant" hypertension responded to parenteral and oral administration of the preparations in a variable fashion; some cases were later well controlled with oral doses, while others were only partially controlled; two failed to be affected more than temporarily. The malignant stage was altered favorably in all but two.

The method was practical for use at home, in patients intelligent enough to exploit its advantages. It represents a way of controlling hypertension, but in no sense is it a "cure."

Long-term results cannot be evaluated until much time has elapsed. During this short-term study some of the pathological signs secondary to chronic hypertension regressed in the direction of normal.

The "toxic" effects of hexamethonium are attributable to the primary action of the drug itself, i. e., autonomic paralysis. The "toxic" effects of hydrazinophthalazine are attributable to its action in suppressing histaminase activity. The "toxic" effects of both drugs in combination are caused by severe hypotension rapidly induced in subjects with organic vascular disease causing ischemia of brain, myocardium, or kidney.

While administration of these drugs can control most cases of "benign" hypertension at normal or near-normal levels, there remains an increment of malignant hypertension which is not attacked.

ADDENDUM

Subsequent experience with 60 patients taking these drugs for 10 to 28 weeks and continuing has shown that 30 have sustained normotensive levels. Of 22 in the malignant stage, 8 are normotensive and 12 slightly hypertensive; the malignant stage has regressed in all instances. Tolerance has not appeared. Three patients in severe malignant stages have died while controlled by treatment, two of pneumonia and one of renal insufficiency. Six in malignant stages have discontinued medication voluntarily or on advice of a physician; all have died of the effects of hypertension. The method is limited in effectiveness when moderate renal insufficiency has been present.

The following physicians allowed patients to be treated: Dr. Harry L. Alexander, Dr. Edward L. Massie, Dr. Sim F. Beam, Dr. Keith S. Wilson, Dr. Samuel B. Grant, Dr. Joseph S. Noah, Dr. Ernest T. Rouse, Dr. Michael M. Carl, Dr. I. Jerome Flance, Dr. Margaret L. Gilden, Dr. Bruce Kennamore, and Dr. Melvin L. Goldman. Elizabeth F. Perry drew the charts. Julia E. Finn helped in computing the data. Dr. Melvin L. Goldman, Dr. Greta H. Camel, Dr. Richard F. Huck, and Dr. William H. Stimpson followed some of these patients from time to time.

HISTOPLASMOSIS IN EPIDEMIC FORM

A Follow-up Study

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HISTOPLASMOSIS in its acute form occurs either as a benign or as a fulminating fatal disease. Previous reports of the disease indicate that it has occurred sporadically and not in epidemic form. We have had the opportunity to follow up 1 of 26 cases of diffuse pneumonitis which occurred as an epidemic at Camp Gruber, Okla., in 1944 and was reported as "An Unusual Pulmonary Disease." [1] This case is presented in detail, since we feel that it will aid in establishing the origin of this epidemic as an infection with Histoplasma capsulatum.

REPORT OF A CASE

K. W., a white man, was admitted to the United States Army Station Hospital, Camp Gruber, Okla., on March 28, 1944, acutely ill, complaining of chills and fever, sweating, generalized aching, headache, and nonproductive cough. In the next few days 25 other soldiers in his company were admitted to this hospital with similar complaints.

Careful analysis of the histories indicated that there was one common factor involved in each of these 26 admissions, namely, that in the course of a military exercise on March 17, 1944, all the men had been required to stay in an abandoned storm cellar for varying periods from midnight to 8:00 a. m. The patient's previous history was essentially normal, and a roentgenogram of the chest taken at the time of induction July 30, 1943, disclosed no evidence of pulmonary disease.

Physical examination on admission revealed a 36-year-old white man who was acutely ill. The temperature was 102 F., the pulse rate, 90, and the respiration rate, 18. The results of the remainder of the physical examination were essentially normal. Roentgen inspection of the chest (Fig. 1), however, revealed a diffuse mottling throughout both lung fields, with bilateral enlargement of the hilar nodes. The white blood cell count was 9,800, with 90% polymorphonuclear leucocytes. Results of urinalysis were normal. The sedimentation rate (Cutler method) varied from 15 to 28 mm. per hour during the first two weeks of illness. Sputum studies revealed yeast-like forms, identified as Candida albicans, which were found to be nonpathogenic to mice, guinea pigs, and rabbits. No tubercle bacilli were found on repeated culture and guinea-pig inoculation. The Mantoux test, employing a 1:10,000 dilution of old tuberculin, gave a

From the Veterans Administration Regional Office, Brooklyn.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Cain, J. C.; Devins, E. J., and Downing, J. E.: Unusual Pulmonary Disease, Arch. Int. Med. **79**:626-641 (June) 1947. A New Pulmonary Disease Entity? editorial, J. A. M. A. **139**:232 (Jan. 22) 1949.

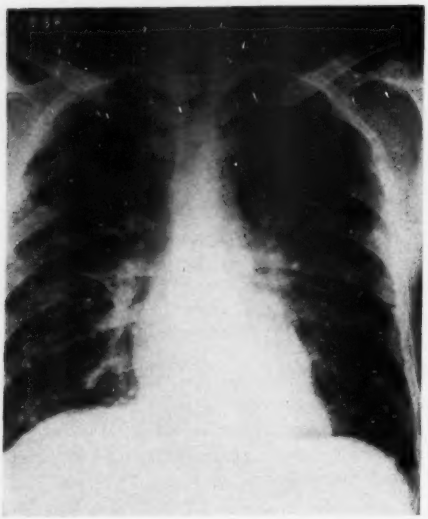

Fig. 1.—Roentgenogram of chest taken on April 1, 1944, reveals disseminated infiltrations throughout both lung fields, with enlargement of hilar nodes.

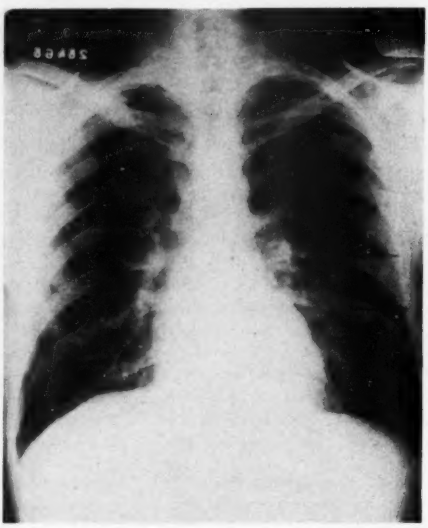

Fig. 2.—Roentgenogram of chest taken Oct. 26, 1944, reveals resolution of soft infiltrations. Fibrotic nodules of varying size are now noted throughout both lung fields. Hilar nodes have decreased in size.

negative reaction. The coccidioidin skin test, 1:100 dilution, performed in the second week of illness, gave a negative reaction. Agglutination tests for brucellosis, tularemia, and typhoid and serologic tests for psittacosis gave negative results. The reactions on serologic tests for histoplasmosis were also negative. This condition was diagnosed as an interstitial pneumonia, type undetermined.

The acute phase of the disease lasted one week, during which time the temperature fluctuated between 102 and 104 F. Thereafter, the fever gradually subsided and the patient made a complete recovery. Serial roentgenographic studies of the chest revealed that the soft, mottled densities in both lung fields reached their maximum intensity within two weeks, after which resolution became apparent. Six weeks after onset the chest roentgenogram revealed miliary or somewhat larger fibrotic nodules scattered diffusely throughout both lung fields without evidence of calcification. For the next six months further change was imperceptible, and the fibrotic nodules were considered to be permanent residuals (Fig. 2).

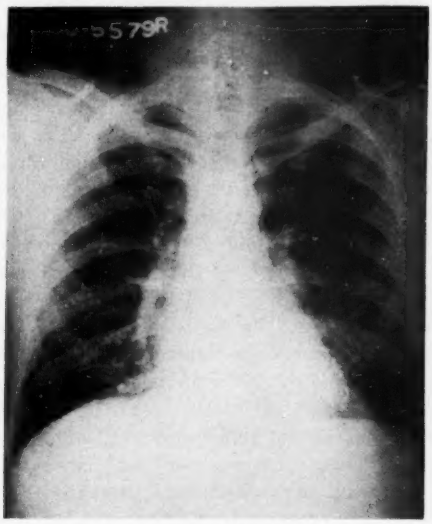

Fig. 3.—Roentgenogram of chest taken Nov. 12, 1950, reveals calcifications disseminated throughout both lung fields.

A follow-up physical examination performed six years later disclosed an essentially normal condition. Roentgenologic studies of the chest (Fig. 3) at this time, however, revealed miliary and somewhat larger-sized calcified nodules scattered diffusely throughout both lung fields. Many of these nodules had a dense calcific center and a lighter noncalcified periphery, producing a "halo" effect. This roentgen picture was so strongly suggestive of the end-stage of pulmonary histoplasmosis that appropriate studies were made to confirm this diagnosis. Sputum yielded no acid-fast bacilli or fungi on smear and culture. A skin test with histoplasmin (1:1,000) gave a strongly positive reaction (4+). Reactions to a skin test with coccidioidin (1:100) and to a Mantoux test, using a 1:1,000 dilution of old tuberculin, were negative. A complement-fixation test for histoplasmosis, using the yeast phase antigen of H. capsulatum, was positive to a titer of 1:140 and negative for other fungi.

COMMENT

This report deals with one of a group of cases of acute pulmonary disease in an epidemic of unknown causation. We have been able to demonstrate in a follow-up

study of this patient six years later the picture of pulmonary histoplasmosis, which suggests that the other members of the affected group also had a benign form of histoplasmosis.

Other epidemics of acute, diffuse pneumonitis essentially similar to this one have been reported from time to time, and it is worth while to note that in none of them was the cause ever established. Nauen and Korns [2] reported the first of these epidemics of miliary pneumonitis. In 1938 a group of 23 men was engaged in demolishing the tower of an old school building in Plattsburg, N. Y., which was filled to about 4 ft. (1.2 meters) with dead pigeons and their droppings. Seven to fourteen days following their exposure to this dust all displayed an acute febrile illness and bilateral pneumonitis with hilar enlargement. Calcifications appeared in the central portion of the pulmonary infiltrations 8 to 30 months after onset. Idstrom and Rosenberg [3] reported an outbreak from Camp Crowder, Mo., in 1944. Forty soldiers assigned to clean barns, dusty farm houses, and chicken coops prior to installation of Signal Corps equipment exhibited varying degrees of the same type of bilateral pulmonary infiltrations with hilar adenopathy. The roentgenographic findings persisted in some during the observation period of six months. Again, no cause was assigned to these cases. Still another epidemic occurred in September, 1947, when 21 of 25 persons engaged in a treasure hunt in an abandoned chalk mine in Arkansas had diffuse, bilateral pneumonitis. This was reported as "Cave Sickness, A New Disease Entity?" [4] The incubation period in these cases was 4 to 14 days, with sudden onset of chills, fever, headache, generalized aches and pains, and slight cough. Finally, another epidemic of miliary pneumonitis of unknown causation was reported by Feldman and Sabin.[5] Here 12 men were exposed to the dust of pigeon excreta while demolishing an old abandoned water tower in Cincinnati, in July, 1947. After an incubation period of 5 to 14 days, all had clinical manifestations varying from a mild transitory "grippe" to a severe prostrating disease lasting almost three weeks. Chest roentgenograms revealed a diffuse, fine granular infiltration throughout both lung fields. A follow-up study [6] of 18 months did not reveal the development of pulmonary calcifications.

It is to be noted that three of these epidemics were reported from the so-called endemic area outlined for histoplasmosis, which includes the states of Tennessee, Kentucky, Arkansas, Missouri, and parts of Ohio, Illinois, Kansas, Louisiana, and Oklahoma. Within these states, histoplasmin-positive and tuberculin-negative cases with pulmonary calcifications are especially prevalent and have been attributed

2. Nauen, R., and Korns, R. F.: A Localized Epidemic of Acute Miliary Pneumonitis, Associated with the Handling of Pigeon Manure, read at Annual Meeting of American Public Health Association, New York, October, 1944. White, F. C., and Hill, H. E.: Disseminated Pulmonary Calcifications, Am. Rev. Tuberc. **62**:1-16, 1950.

3. Idstrom, L. G., and Rosenberg, B.: Primary Atypical Pneumonia, Bull. U. S. Army M. Dept. **81**:88-92, 1944.

4. Washburn, A. M.; Tuohy, J. H., and Davis, E. L.: Cave Sickness: New Disease Entity? Am. J. Pub. Health **38**:1521-1526, 1948.

5. Feldman, H. A., and Sabin, A. B.: Pneumonitis of Unknown Etiology in Group of Men Exposed to Pigeon Excreta, abstracted, J. Clin. Invest. **27**:533, 1948.

6. Felson, B.; Jones, G. F., and Ulrich, R. R.: Roentgenologic Aspects of Diffuse Miliary Granulomatous Pneumonitis of Unknown Etiology, Am. J. Roentgenol. **64**:740-746, 1950.

to the end-stage of histoplasmosis.[7] The greatest incidence of histoplasmosis in its clinical form also is within this region. With further skin-testing and mass roentgen surveys, this endemic area will probably be enlarged. A common feature of these outbreaks was the exposure to dust, especially that associated with the habitation of pigeons, chickens, and rodents. Emmons and co-workers [8] have found H. capsulatum occurring naturally in dogs, rats, mice, ferrets, and horses and have cultured the organism from the soil where naturally infected rats have abounded. Due to the close association of rodents and fowl in fields, farms, chicken houses, and old buildings, it is obviously impossible to state whether one or both were responsible for the contamination of the soil and the source of the infection. It may be stated, however, that exposure to infected organic dust within the endemic area has led to pulmonary infection. In our case, efforts to obtain the offending organism from the soil of the storm cellar were fruitless. Recent advancement in cultural technique may well account for the successful isolation of H. capsulatum from soil by other observers.

The diagnosis of histoplasmosis in the generalized and usually fatal case is made by culture of sputum, gastric contents, bone marrow, and lymph nodes removed for biopsy.[9] In the benign form, the diagnosis is more difficult to establish because the organism is not as readily isolated. The skin test and the complement-fixation test frequently give negative reactions in the acute phase and early convalescence of the disease, adding to the difficulty in establishing the diagnosis.[10] It is, therefore, not surprising that the serologic studies for histoplasmosis during the acute phase of our case gave negative results. It is advisable to follow these patients over a prolonged period with repeated tests in order to demonstrate the development of skin sensitivity to histoplasmin and a positive complement-fixation reaction. However, in the epidemics cited above, repeated skin tests and complement-fixation tests have not been performed after recovery of the patients, and, for this reason, reversal of the anergic phase has not been noted.

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7. (*a*) Christie, A., and Peterson, J. C.: Pulmonary Calcification in Negative Reactors to Tuberculin, Am. J. Pub. Health **35**:1131-1147, 1945. (*b*) Palmer, C. E.: Geographic Differences in Sensitivity to Histoplasmin Among Student Nurses, Pub. Health Rep. **61**:475-487 1946. (*c*) Peterson, J. C., and Christie, A.: Histoplasmosis and Pulmonary Calcifications, Am. Rev. Tuberc. **57**:361-366, 1948. (*d*) Long, E. R., and Stearns, W. H.: Physical Examination at Induction: Standards with Respect to Tuberculosis and Their Application as Illustrated by Review of 53,400 X-Ray Films of Men in Army of the United States, Radiology **41**:144-150, 1943.

8. Emmons, C. W.; Bell, J. A., and Olson, B. J.: Naturally Occurring Histoplasmosis in Mus Musculus and Rattus Norvegicus, Pub. Health Rep. **62**:1642-1646, 1947. Emmons, C. W., and Ashburn, L. L.: Histoplasmosis in Wild Rats: Occurrence and Histopathology, ibid. **63**:1416-1422, 1948. Emmons, C. W.: Isolation of Histoplasma Capsulatum from Soil, ibid. **64**:892-896, 1949.

9. (*a*) Bunnell, I. L., and Furcolow, M. L.: Report on 10 Proved Cases of Histoplasmosis, Pub. Health Rep. **63**:299-316, 1948. (*b*) Parsons, R. J., and Zarafonetis, C. J. D.: Histoplasmosis in Man: Report of 7 Cases and Review of 71 Cases, Arch. Int. Med. **75**:1-23 (Jan.) 1945.

10. Peterson and Christie.[7c] Bunnell and Furcolow.[9a] Zahn, D. W.: Pulmonary Infiltration Associated with Sensitivity to Histoplasmin: Report of Case, Am. Rev. Tuberc. **59**:636-642, 1949.

The chest roentgenogram in the acute stage of histoplasmosis is not characteristic.[11] However, in the presence of a disseminated pneumonitis with or without enlargement of the hilar nodes, this diagnosis should be given serious consideration. Repeated roentgen examinations will disclose resolution of the lesions and development of residual fibrosis, and long-term follow-up roentgen studies may reveal calcifications as the end-stage of this condition. In the various epidemics the patients have not been followed for periods longer than 18 months. Such periods of observation are too short to demonstrate the development of calcification in all cases. Several of the patients involved in these outbreaks of disseminated pneumonitis showed a complete clearing of the infiltrations in a relatively short time. This course depends upon two factors: the concentration of the infecting organisms and the reaction of the host. If the dosage of the infecting organism is small, the inflammatory reaction in the pulmonary parenchyma will be mild and resolution will occur. However, if the dosage is great, the resultant inflammatory reaction will be intense and central necrosis of the lesions may take place, to be followed by fibrosis and calcification during the healing stage.[12] When the calcification is confined to the center of the lesion, the so-called halo effect may be demonstrated on the roentgenogram.[13] Eventually, this "halo" will disappear, if the calcification of the lesions becomes complete.

SUMMARY

A follow-up study on one of a group of cases previously reported under the title "An Unusual Pulmonary Disease" is presented.

Subsequent roentgen examinations, skin tests, and complement-fixation tests indicate that this case represents the end-stage of acute, benign histoplasmosis.

It is suggested, therefore, that the remaining persons in this epidemic also were infected with Histoplasma capsulatum.

Attention is drawn to four epidemics of a similar nature in which the causation has never been established. It is hoped that this report will stimulate further follow-up study of these cases.

Dr. Elizabeth L. Hazen, of the Division of Laboratories and Research, New York State Department of Health, performed the serologic tests for histoplasmosis.

11. Holt, J. F.: Roentgenologic Pulmonary Manifestations of Fatal Histoplasmosis, Am. J. Roentgenol. **58**:717-723, 1947.

12. Ash, J. E., and Spitz, S.: Pathology of Tropical Diseases, Philadelphia, W. B. Saunders Company, 1945, pp. 156-157 and 184-185.

13. Furcolow, M. L.; Mantz, H. L., and Lewis, I.: Roentgenographic Appearance of Persistent Pulmonary Infiltrates Associated with Sensitivity to Histoplasmin, Pub. Health Rep. **62**:1711-1718, 1947. Silverman, F. N.: Pulmonary Calcification, Am. J. Roentgenol. **64**:747-764, 1950.

MENTAL CHANGES ASSOCIATED WITH HYPERPARATHYROIDISM

Report of Two Cases

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AND
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WHEN THE classic clinical picture of hyperparathyroidism is present, the diagnosis is usually readily made. The most bizarre clinical pictures are produced when the calcium levels are extremely high, or, in other words, when the picture of calcium poisoning is present. This has been referred to as "parathyrotoxicosis."[1] These are the cases that may result in sudden death and are definitely medical emergencies. We have had an opportunity to observe two such cases in which the primary manifestations were psychic. In both cases the mental disturbances produced such an unusual picture that the diagnosis was overlooked for several months. In one of these cases this delay led to almost disastrous consequences.

Although much has been written about hyperparathyroidism, comparatively little attention has been devoted to its effects on mental processes. For this reason, and since any toxic signs are danger signs in this disease, we thought it important to report these two cases.

The mechanism of this psychosis is not known. We do know that the calcium ion is closely related to nerve function. Albright and Reifenstein[2] cited the work of Hannon, Shorr, McClellan, and DuBois,[3] in which it was shown that twice the amount of current was required to excite an isolated nerve in a patient with this disease. Of course, the minute particles of metastatic calcium sometimes found in the brain tissue may play a part. Other evidence of nervous and mental disorders has been shown both in observations of patients and in animal experiments.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own studies and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Waife, S. O.: Parathyrotoxicosis: The Syndrome of Acute Hyperparathyroidism, Am. J. M. Sc. **218**:624-635 (Dec.) 1949.

2. Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease: Selected Studies, Baltimore, Williams & Wilkins Company, 1948.

3. Hannon, R. R.; Shorr, E.; McClellan, W. S., and DuBois, E. F.: A Case of Osteitis Fibrosa Cystica (Osteomalacia?) with Evidence of Hyperactivity of the Parathyroid Bodies: Metabolic Study, J. Clin. Invest. **8**:215-227 (Feb.) 1930; cited by Albright and Reifenstein.[2]

Collip [4] reported a psychic depression in the animals receiving parathormone when the blood calcium exceeded the normal level by from 2 to 3 mg. In 1932, Lowenburg and Ginsberg [5] reported progressive listlessness, lethargy, and apathy in a 5-year-old boy who received by mistake 100 mg. of parathyroid extract for six days. Oliver [6] described drowsiness and mental retardation in two cases which ended fatally, and he cited a case reported by Schrumpf and Harbitz [7] in which disorientation was marked but cleared following removal of two parathyroid adenomata. Hanes [8] described a changing mental picture as a patient progressed to death from hyperparathyroidism. Chaplin and associates [9] in their report on vitamin D intoxication referred to mild psychosis in patients with elevated serum calcium. In a review of the literature in 1942, Eitinger found 7 cases of 50 that showed evidence of psychic changes.[10] Five of these seven occurred in the Scandinavian countries. In all these cases, except those cited by Eitinger and the one reported by Schrumpf and Harbitz, the mental changes as described were manifested just prior to the patient's death.

REPORT OF CASES

CASE 1.—A 55-year-old white man, a retired merchant seaman, was admitted to Lawson Veterans Administration Hospital, Chamblee, Ga., on Feb. 23, 1951, for examination and observation for pension-rating purposes. His complaints were multiple and included (1) a two-year history of recurrent colicky pain in the right lower abdominal quadrant, requiring a "shot" for relief and associated with urgency, frequency, and nocturia (four to six times a night), with burning, hesitancy, dribbling, incontinence, and cloudiness but with no history of hematuria or stones; (2) pain in the chest on exertion, of 15 to 20 minutes' duration, characterized by burning sensation in the right xiphoid area, worse on an empty stomach, relieved by taking food or sodium bicarbonate, and accompanied with dyspnea, sweating, etc.; (3) occipital headaches and a sense of pressure in the head since an accidental head injury in 1936. He described episodes of dizziness and unconsciousness lasting 15 to 20 minutes not accompanied with convulsions. All these complaints were overshadowed by the apparent paranoid personality of the patient, as manifested by repeated references to "evil influences" affecting his life; his feeling that his "lack of wealth" was responsible for people plotting against him; "voices" and "heavenly music" either comforting him or warning him of impending doom; "voices" trying to force him to go "closer and closer to high or dangerous places" so "they could kill him."

Results of Physical Examination.—All vital signs were normal. The patient was well developed and slightly obese. He was oriented to time and place but at times seemed to be out of contact with reality. Except for a 2.5-cm. oval, depressed area in the frontoparietal area of the skull and the absence of the first four toes of the right foot, the results of general physical examination were normal. Of interest was the vivid description of a lion in the streets and a bus hitting and killing a man (the patient); these illustrations were precipitated by the examiner applying pressure and massage over the orbits while questioning the patient.

4. Collip, J. B.: The Parathyroid Glands, Medicine **5**:1-57 (Feb.) 1926.

5. Lowenburg, H., and Ginsberg, T. M.: Acute Hypercalcemia: Report of a Case, J. A. M. A. **99**:1166 (Oct. 1) 1932.

6. Oliver, W. A.: Acute Hyperparathyroidism, Lancet **2**:240-244 (July 29) 1939.

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8. Hanes, F. M.: Hyperparathyroidism Due to Parathyroid Adenoma with Death from Parathormone Intoxication, Am. J. M. Sc. **197**:85-90 (Jan.) 1939.

9. Chaplin, H., Jr.; Clark, L. D., and Ropes, M. W.: Vitamin D Intoxication, Am. J. M. Sc. **221**:369-378 (April) 1951.

10. Eitinger, L.: Hyperparathyroidism with Mental Changes, Nord. med. **14**:1581-1585 (March) 1942.

Laboratory and Roentgen Data.—The hemoglobin concentration, white blood cell count, differential count, and urine were all normal. Nonprotein nitrogen was 42 mg. and cholesterol 288 mg. per 100 cc. Results of stool examinations were normal. Serum calcium was 14 mg. per 100 cc. on two occasions. Phosphorus measured 2.1 and 2.3 mg. per 100 cc.; alkaline phosphatase was 6.3 and 6.5 Bodansky units. Total protein was 6.5 gm., with albumin of 4.1 gm. and globulin of 2.4 gm., per 100 cc. Spinal fluid had normal dynamic pressure with one red blood cell per field and 65 mg. of total protein and 6.1 mg. of calcium per 100 cc. Quantitative urine calcium excretion was 715 mg. in 24 hours, with the patient on a low-calcium diet. Blood and spinal fluid serologic tests for syphilis gave negative results. An electrocardiogram was normal.

Roentgenograms of skull, spine, feet, gastrointestinal tract, abdomen, and urinary tract revealed no abnormalities.

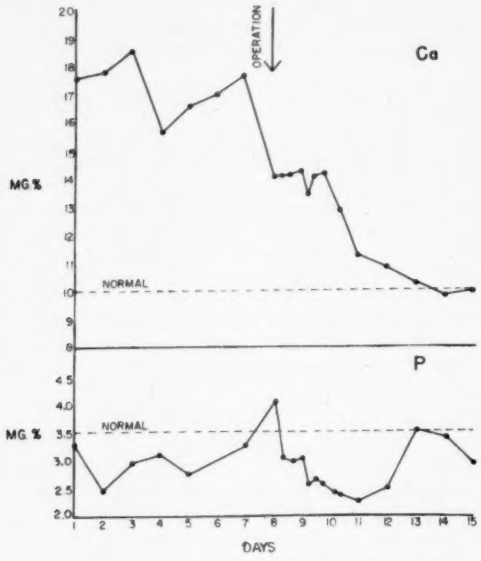
Hospital Course and Treatment.—The patient seemed to shy away from people and at times lost contact with reality. Frequent interviews brought out more psychotic manifestations. An exploratory operation for parathyroid tumor was carried out on March 15, 1951, and a 3- by 1.5-cm. adenoma was removed. No other adenomata were seen. The postoperative course was uneventful. On the day following the operation the blood calcium was 10.1 mg., and phosphorus was 3.0 mg., per 100 cc. There were no signs of tetany, postoperatively. Subsequent interviews with the patient revealed remarkable mental clearing. He remembered the feelings of persecution, hearing voices, etc. At the time of discharge on March 29, 1951, he was associating with the other ward patients and expressed no further mental confusion, hallucinations, or illusions. His serum calcium was 10 mg. and serum phosphorus 2.6 mg. per 100 cc. Alkaline phosphatase measured 6 Bodansky units. Urine calcium was 315 mg. in 24 hours. Results on follow-up examinations have proved to be normal.

CASE 2.—The patient was a 52-year-old white man who had been in good health until six months before admission. He began to tire easily, became nervous, had insomnia, and felt that his memory was failing him. When at work, he realized that his thinking processes were slower than usual. For two months before admission he had a low fever (temperature elevation to about 100 F.) each night. He had recurrent, catchy pains in the left side of the chest and severe headaches. He had sharp cramping pains in the right leg and right foot lasting two to three minutes. His appetite remained good, and he ate a normal diet. There was no nausea and vomiting. About one month before admission definite and serious personality changes developed. His family said that he lived in a constant state of confusion. He was forgetful and irritable and frequently had great outbursts of temper. He would often speak of entirely unrelated subjects as if he had just awakened from a dream. He began to drink heavily, although he had been only a moderate drinker previously. He frequently used obscene language and was loud, boisterous, and domineering at all times. This period was marked by a rapidly changing picture of great depression and great elation. This personality pattern progressed rapidly to the point that the patient became completely unmanageable. At times he rested for hours seemingly exhausted. By the time he was admitted to the hospital he was completely out of touch with reality. He required large doses of sedatives and physical restraint. He became drowsy after two weeks in the hospital and gradually slipped into a coma. His entire illness was marked by great thirst and polyuria.

Results of Physical Examination.—The temperature was 101 F., the pulse rate, 100, and the respiration rate, 16. The blood pressure was 190/110. The patient was a moderately obese man speaking incoherently and obviously greatly disturbed. There were signs of dehydration. The liver was enlarged about 4 cm. below the right costal margin and was smooth and nontender. This was the only positive physical finding besides the elevated blood pressure and the obvious delirium.

Laboratory Data.—The patient had a moderate anemia with normal leucocyte and differential counts. The admission nonprotein nitrogen was 100 mg. per 100 cc. but fell to a range between 50 and 60 mg. after he was given adequate fluids. Repeated urinalyses gave normal results, except for a very low specific gravity. The test with sulfobromophthalein (bromosulphalein®) sodium showed 15% retention in 45 minutes. A test with phenolsulfonphthalein showed 15% excretion in one hour. At first, the blood calcium was 19 mg. and phosphorus

2.24 mg. per 100 cc.; alkaline phosphatase was 5.4 King-Armstrong units. The spinal fluid was normal. The blood calcium level varied thereafter between 16 and 18 mg. per 100 cc. The phosphorus level was usually about normal. The phosphatase value rose gradually to 10.9 King-Armstrong units. Total serum protein was 6.4 gm. The serum sodium ranged between 120 and 130 mEq. and the serum potassium between 3 and 4 mEq. per liter. Urinary excretion of calcium



Upper graph shows rapid fall of blood calcium to normal within 48 hours after operation. Lower graph shows blood phosphorus levels.

Rapid Fall in Urinary Excretion of Calcium to Normal Level in Twenty-Four Hours After Operation

Date	Mg. Ca/24 Hr.	Mg. Ca/6 Hr.
2-18-50 (postoperative)		
12-6 p. m.	...	65.5
6-12 p. m.	...	24
12-6 a. m.	...	33
6-12 a. m.	...	30
Total	152	
2-6-50	927	..
2-10-50	620	..
2-13-50	790	..
2-16-50	800	..
2-17-50	740	..

ranged between 700 and 800 mg. per 24 hours. A roentgenogram of the skull showed very early demineralization; the rest of the bony survey was normal. The results of bone marrow studies and the electrocardiogram were normal.

Course in Hospital.—The patient's delirium necessitated constant care. He refused to eat or take fluids. It was necessary to give him 3,000 to 4,000 cc. of isotonic sodium chloride solution and 2 to 4 gm. of potassium chloride each day to keep his sodium and potassium levels near a normal range. He was given sodium citrate solution intravenously daily; this seemed to lessen

his delirium.[11] Uremia was strongly suspected on admission because of the hypertension and the elevated nonprotein nitrogen level. However, this fell to 40 and 50 mg. per 100 cc., and with the results of other studies this diagnosis seemed unlikely. The presence of some type of alcoholic psychosis was considered.

When the diagnosis of hyperparathyroidism became fairly certain, an exploration of the neck was done. No tumor was found. Although roentgenographic studies failed to reveal any evidence of a tumor in the mediastinum, the anterior mediastinum was explored four days after the operation on the neck. A parathyroid adenoma 3 cm. in diameter was found near the arch of the aorta. Serial blood levels of calcium and phosphorus were determined before and immediately after the operation. These showed a rapid drop to normal values within 48 hours (Figure). The urinary calcium excretion level was determined on six-hour specimens, and this became normal 24 hours postoperatively (Table). The patient was quieter, and his delirium had almost disappeared by the time he had recovered from anesthesia. Twenty-four hours after the operation he was his normal self, according to his family. He remembered nothing of his previous three or four weeks' experiences. He made an uneventful recovery and has returned to his business. After one year, his calcium levels have remained normal and his mental status has remained clear.[12]

SUMMARY

Two cases of hyperparathyroidism are reported with marked mental changes as their major symptoms. The classic findings, such as demineralization of the bones, fractures, bone pains, and marked renal calcinosis, were not present. Operation was performed in both cases, and parathyroid adenomata were removed, with rapid clearing of all mental symptoms. A survey of the literature revealed that this aspect of hyperparathyroidism has not been previously emphasized.

11. Herrman, J. B.; Kirsten, E., and Krakauer, J. S.: Hypercalcemic Syndrome Associated with Androgenic and Estrogenic Therapy, J. Clin. Endocrinol. **9**:1-9 (Jan.) 1949.

12. Dr. F. M. Atkins gave us permission to report this case.

PHYSICAL MEDICINE AND REHABILITATION IN ACUTE MYOCARDIAL INFARCTION

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THERE has been much discussion concerning the management of acute myocardial infarction, and a vast amount of literature has accumulated on this subject. The greater part of this has been a consideration of various therapeutic agents which were or were not of benefit, and of the necessity of bed rest, as well as the time that ambulation should be started.

For the most part, opinion is fairly well crystallized regarding these matters; however, this condition brings into existence other factors which are worthy of consideration. While they do not materially affect mortality, they are vitally concerned with a smooth clinical course, the peace of mind of the patient, and the incidence of anxiety neurosis. All physicians treating acute myocardial infarction are aware of the importance of the following factors: (1) deconditioning during bed rest, with alterations in all physiologic processes; (2) the boredom and impatience created by the slow passage of time; (3) the depression and anxiety resulting from enforced complete bed rest which the patient, owing to lack of understanding, may interpret as indicating he is a permanent cardiac invalid; (4) the symptoms and anxiety which frequently attend the transition from bed rest to activity when not closely supervised.

Activities to eliminate or decrease these factors would be of great advantage to the patient. It is our impression that the items listed above are of sufficient importance to justify therapeutic effort when possible.

It was felt by one of us (L. A. B.) that the facilities available at this hospital presented an unusual opportunity for initiating a program which would attempt a therapeutic correction with respect to these matters. In cooperation with the physical medicine and rehabilitation service, a program involving both physical and occupational therapy was organized and put into effect as a routine part of the management of all patients with acute myocardial infarction. This program has now been in effect since June, 1948, and the results have been sufficiently gratifying to justify this report.

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OUTLINE OF THE PROGRAM

Prescribed, controlled activities, including ambulation, are important in the rehabilitation of these patients. An activity program with ambulation leading to increased work capacity for patients with acute myocardial infarction will be described. However, this program with modifications for the individual patient can be instituted in other types of cardiac disorders. The program is planned on a six weeks' basis, which covers the average period from admission to discharge. However, the six-week activity classification cannot always be adhered to rigidly. In accordance with the advice of the physician and depending upon the progress and complications encountered in each case, the program is individually adjusted. The activity classification refers to the amount of activity the patient can accomplish at a specific time which will increase work capacity consistent with his cardiac reserve. Patients may be kept on a certain week's activity schedule for a period longer than a week if any untoward symptoms or complications develop. On the other hand, if a patient has advanced to a certain week's activity program, he may be reverted to a previous week's activity if his progress has not been favorable and/or complications have developed. If the patient's recovery is slow, his activity participation will not advance as rapidly from one week to the next. The day on which the patient is placed on the rehabilitation program is chosen by the physician in charge. Obviously the patient must have recovered from shock, pain must be minimal or absent, and he must be resting comfortably without dyspnea or other disturbing symptoms. During the first week, "complete bed rest" is insisted upon and the active program is not undertaken. However, during this week, if the patient's condition is such that the physician believes it advisable, the patient is contacted by the occupational and physical therapists, who outline and discuss the prospective program with the patient. It is our opinion that the psychological effect of this interest of the therapist in him and the fact that already a program for his reactivity is being planned are of great value in supporting the patient's morale.

Not until the second week does the active program get under way. The immediate objectives of this program are as follows:

1. *To Teach the Patient Both Psychological and Physical Rest.*—A person who has been active finds it difficult to relax and rest when suddenly restricted to being an absolute bed patient. This is made more difficult by the anxiety created by a "heart attack." The restlessness and tension can be alleviated through diverting attention and energy to constructive supervised activity.

2. *To Instill a Proper Mental Attitude in the Patient Toward His Illness and to Prevent the Development of Anxiety Neurosis.*—The patient may react unfavorably to the suddenly enforced complete bed rest by adopting the attitude that he has suffered such severe permanent cardiac damage that physical activity can never be undertaken without great danger. Infrequently this hopeless attitude may persist into the period of convalescence, so that despair and anxiety in themselves cause indefinite invalidism. The conducted rehabilitation program is designed so that, from the first, the patient is impressed with the idea that he will again become active by way of planned supervision. In this way convictions of permanent invalidism are prevented from becoming established. The program emphasizes to the patient that he

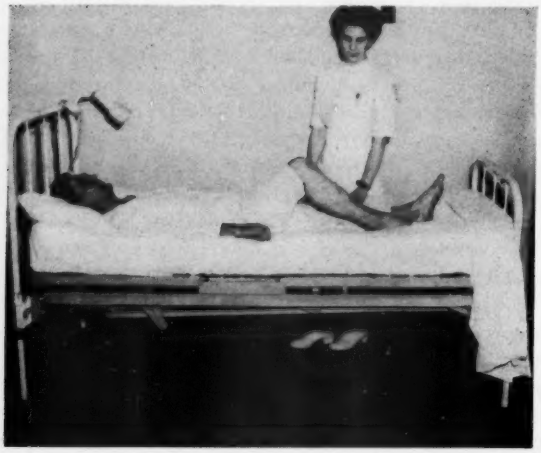

Fig. 1.—Patient with myocardial infarction. Active exercise of lower extremities as part of second week's physical therapy procedures.

Fig. 2.—Patient with myocardial infarction making link belt as part of second week's occupational therapy activities.

Fig. 3.—Patient with myocardial infarction performing active exercises of lower extremities while sitting over edge of bed as part of fourth week's physical therapy procedures.

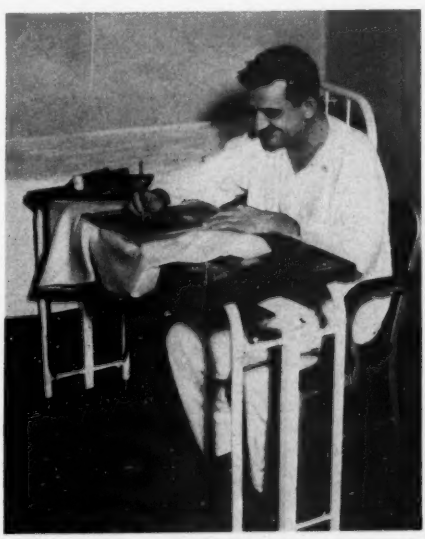

Fig. 4.—Patient with myocardial infarction textile stencilling while sitting in chair at bedside as part of fifth week's occupational therapy activities.

Fig. 5.—Patient with myocardial infarction walking up and down stairs as part of sixth week's physical therapy procedures.

Fig. 6.—Patient with myocardial infarction operating foot-powered printing press as part of sixth week's occupational therapy activities.

Outline of the Rehabilitation Program in Myocardial Infarction

Week	Physical Therapy	Occupational Therapy
1st	None Complete bed rest; interviews by rehabilitation staff if patient's condition permits	None Complete bed rest
2d	Teach patient to relax Supervised exercises; include diaphragmatic breathing exercises 1st and 2d days Flex and extend toes—relax Dorsiflex and plantarflex ankle—relax Make fist—open—relax Extend and flex wrist—relax Repeat above exercises 5 times b.i.d. 3d and 4th days Increase above exercises to 10 times b.i.d. Add isometric contractions of quadriceps group Flex and extend elbows Actively place hands behind head 1 time b.i.d. Repeat above exercises 10 times b.i.d. 5th, 6th, and 7th days Add to above exercises—flex knees to 90° angle by sliding foot on bed (Fig. 1) Repeat 10 times b.i.d.	Activities for upper extremities (limited shoulder movements) Start with 15 min. b.i.d. and increase by 2d day to 30 min. b.i.d., making link belts, leather punching and lacing, rake knitting, etc. (Fig. 2)
3d	1st and 2d days Above exercises with the addition of isometric contraction of gluteal muscles Repeat 10 times b.i.d. 3d, 4th, and 5th days Above exercises with the addition of all active movements of the shoulders and hips Repeat 5 times b.i.d. 6th and 7th days Exercises as above, increase to 10 times b.i.d. Sitting over edge of bed with feet resting on chair, pillows behind back for support 15 min. b.i.d.	Activities for both upper extremities and shoulders, 1 hr. b.i.d. with patient gradually elevated to a sitting position in bed doing wire jewelry making, textile stencilling and painting, photo tinting, metal foil tooling, leather tooling, etc.
	Educational therapy, if desired and indicated, such as selective reading, writing, and typing	
4th	1st, 2d, and 3d days Above exercises 10 times b.i.d. 4th day As above, with the addition of active movements of the shoulders, hips, and knees in a sitting position 10 times b.i.d. (Fig. 3) 5th, 6th, and 7th days Walks for 3 to 5 min. along bedside b.i.d. Bathroom privileges Observe posture and gait	Activities for both upper extremities and shoulders with some trunk movements; start with ½ hr. b.i.d. and gradually increase by the 4th day to 1 hr. b.i.d. Activities with patient sitting over edge of bed with feet resting on chair, pillows behind back for support, and working on bedside table Activities as above with addition of drawing, plastic projects, advanced jewelry making, crocheting with heavy materials, wood chipping and carving, table weaving, etc., b.i.d. 5th, 6th, and 7th days Above activities with patient sitting in chair, 1 hr. b.i.d.
5th	Progressive walking, measured distances, depending upon patient's reactions 1st day, 50 yd. b.i.d. 2d day, 100 yd. b.i.d. 3d day, 200 yd. b.i.d. 4th day, 300 yd. b.i.d., and for balance of hospital stay May sit up in chair in room ½ hr. t.i.d. at mealtimes	Activities same as for 4th week; however, patient sits in chair at bedside 1½ hr. b.i.d., part of which time he stands Activities as above, with addition of ceramics, small hooking projects, braid weaving, wedging clay, etc. (Fig. 4)
	Vocational advisement and guidance	
6th	Walking 300 yd. b.i.d. Add walking up and down 3 standard stairs, under supervision, using handrails (Fig. 5) 1st day, 3 steps up and down b.i.d. 2d day, 3 steps up and down 2 × (6 steps) b.i.d. 3d day, 3 steps up and down 3 × (9 steps) b.i.d. 4th day, 3 steps up and down 4 × (12 steps) b.i.d. 5th day, 3 steps up and down 5 × (15 steps) b.i.d. From then on can climb full flight of stairs Freedom about ward with short appropriate rest periods during the 6th week	Activities include walking to and from (150 yd. each way) and working in occupational therapy clinic ½ hr. b.i.d. on 1st day and then 1 hr. b.i.d. Activities include working with printing presses, floor looms, bicycle saws, etc., with graded resistance while working with plastics, wood, metal, textiles, etc. (Fig. 6)
	Dietetic counseling before patient is discharged from the hospital	

Criteria for Guidance in the Rehabilitation Activities

1. Pulse	Pulse is taken before, at the completion of, and after a 3-min. rest period following the activity; if there is increase of more than 10 in pulse rate after rest period, this fact is reported to doctor; any further activity is resumed only upon recommendation of doctor; pulse should be taken for 1 full minute and the volume and rhythm noted; any changes are also to be reported to the doctor
2. Respiration	Character and rate of respiration should be noted, and any unusual changes reported to doctor
3. Pain	If any chest or arm pain develops during activity, discontinue activity at once and report this fact to doctor; further activity is resumed only upon recommendation of doctor

Treatment should be promptly discontinued whenever any unusual sign or symptom develops; this should be reported immediately to doctor and information recorded in patient's progress notes

is expected to become ambulant and active after a reasonable time. The participation in such a program, in addition to resulting in physical improvement, enhances the mental and psychological well-being of the cardiac patient.

3. *To Return Muscle Tone and Strength in Order That the Patient May Be Ready for Physical Activity.*—The lack of supervised muscular activity results in marked loss of muscular strength and tone in the average patient. When ambulation is first begun in the fourth week, patients frequently find themselves surprisingly weak and unsteady, and syncope may occur. Limitation of motion of the upper extremities, especially of the shoulders (shoulder-hand syndrome), may result. When active exercise is carried out in a graduated manner, the patient does not notice these difficulties when he first gets up and about. All movements must be done slowly and rhythmically. Ambulation progresses much more smoothly and rapidly when deterioration of the muscle strength and tone has not been allowed to occur. The peripheral circulation is also more stable, so that syncope, palpitation, and other untoward symptoms of circulatory origin are less frequent.

4. *To Aid in Prevention of Peripheral Circulatory Stasis, Which Is Conducive to Phlebothrombosis.*—This factor was considered of great importance when the program was first undertaken. However, due to the established routine and the efficacy of anticoagulant therapy, this factor is now of less importance, but it is still felt that the prevention of stagnation and the stimulation of blood flow in the extremities are valuable adjuncts to anticoagulant therapy.

5. *To Help the Patient Understand His Physical Limitation and How to Control His Activities During Convalescence and After Discharge.*—During the last week of the program the patient works in the occupational therapy kinetic clinic. An estimation of the amount of work capacity without fatigue is obtained. With this information the physician can intelligently plan the future program for the individual patient. Also, the attitude of the patient toward his activity is evident by this time. Encouragement or caution will be stressed, depending on whether the patient has demonstrated himself to be timid or overly aggressive in his acceptance of increasing activity.

Patients can participate in manual arts and educational and corrective therapies when desired and indicated on prescription. Educational therapy can be started for brief periods during the second week in the form of reading. Later, writing or typing can be added.

COMMENT

Since the outlined program was initiated, approximately 300 patients suffering from acute myocardial infarction have been managed accordingly. For the most part, the response and cooperation of the patients to this program have been gratifying. Acceptance has been stressed by Grayson [1] as of great importance in the success of any rehabilitation venture. Among patients suffering from acute myocardial infarction, this factor is rarely lacking. On occasion a patient, because of lack of sufficient insight, may consider the conservative, slowly progressive activity as ridiculous and may resent the close supervision. Rarely, resentment of the patient

1. Grayson, M.: Concepts of Acceptance in Physical Rehabilitation, J. A. M. A. **145**:893 (March 24) 1951.

toward the misfortune of his illness may be so great that it is impossible to create any interest on his part in rehabilitation. However, in the majority of such cases, the program seems to be the most successful means of overcoming this particular mental attitude. In general, the patients welcome and are appreciative of the close attention, encouragement, and progressive nature of the program. It does much to offset the monotony, as well as giving them an objective means of measuring their progress through increasing physical activity.

The need for therapeutic attention to these matters has been stressed by Harrison,[2] and we feel that such a program as herein outlined serves the purpose to the best advantage of the patient.

In addition to what might be considered the psychotherapeutic indications for such rehabilitation, there is adequate evidence that truly physiological benefits are also obtained. The findings of Taylor and associates,[3] relative to the deleterious results of prolonged bed rest on the normal cardiovascular system, are worthy of consideration. It is obvious that in the patient suffering from acute myocardial infarction the problem is far more delicate than in patients whose cardiovascular system is normal. While the regulation of activity will necessarily be much more exact because of decreased cardiac reserve, for the same reason it is even more important to prevent any further deterioration of the cardiac reserve.

It is apparent that during the first 10 days or two weeks following infarction the circulatory load should be maintained at a minimum. After two weeks a very gradual increase in cardiac load may prevent a decrease in the efficiency of the undamaged myocardium; such a decrease has been demonstrated by Taylor and co-workers in normal hearts as the result of absolute bed rest. Thomas and Harrison[4] have questioned the value of prolonged extreme restriction of activity in myocardial recovery.

Visscher[5] has recently reemphasized the fact that restriction below the level of cardiac reserve leads to involutionary changes in structure and function.

The integrity of the peripheral vascular mechanism is as important a consideration as the heart itself, and during the first week or 10 days even more important. The maintenance of adequate peripheral blood flow, blood pressure, and peripheral oxygen exchange during the period of decreased cardiac output is dependent on the maintenance of adequate vasomotor tone, as pointed out by Landis.[6] Prolonged bed rest leaves the peripheral vascular mechanism ineffective for such adjustments. Capillary and venous stasis, in addition to impairment of peripheral metabolic function, contributes to decreased cardiac return and further impairment of the coronary circulation. Gradually increasing muscular activity through the period of

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2. Harrison, T. R.: Abuse of Rest as a Therapeutic Measure for Patients with Cardiovascular Disease, J. A. M. A. **125**:1075 (Aug. 19) 1944.

3. Taylor, H.; Henschel, A.; Brozek, J., and Keys, A.: Effects of Bedrest on Cardiovascular Function and Work Performance, J. Appl. Physiol. **2**:223, 1949.

4. Thomas, W. C., and Harrison, T. R.: Effect of Artificial Restriction of Activity on Recovery of Rats from Experimental Myocardial Injury, Am. J. M. Sc. **208**:436, 1944.

5. Visscher, M. B., in Symposium on Physiological Aspects of Convalescence and Rehabilitation: Cardiac Aspects of Convalescence, Federation Proc. **3**:223, 1944.

6. Landis, E. M., in Symposium on Physiological Aspects of Convalescence and Rehabilitation: Circulatory Adjustments; Peripheral Circulation, Federation Proc. **3**:228, 1944.

bed rest prevents the loss of vasomotor tone to a large extent, thereby adding to the efficiency of the circulation. If the efficiency of the peripheral vasomotor mechanism can be reasonably well maintained during the first few weeks, this will be a great asset when the patient first leaves his bed to become ambulatory. It has been shown by Berry and his co-workers [7] that bed rest for persons with normal cardiovascular systems greatly diminishes the tolerance on the tilt-table test. The heart which has recently undergone infarction is, of course, less able to compensate for inadequacies of peripheral vasomotor tone. Symptoms of weakness, giddiness, and syncope are common when such patients get out of bed. More serious incidents, such as cardiac standstill, ventricular fibrillation, anginal pain, and even sudden death, may occur. It is our experience that such consequences of bed rest can be largely eliminated through adequate preparation of the patient. Such symptoms do much to destroy the confidence of the patient and are not infrequently precipitating factors of anxiety neurosis. Smooth progressive ambulation, free of untoward symptoms, does more to eliminate anxiety and restore the confidence of the patient than any other factor.

Miller and his colleagues [8] and Deitrick and associates [9] have shown that absolute bed rest is conducive to a negative nitrogen balance. Also, there is an increased loss of calcium at such times; Albright and co-workers [10] and Altschule and Rosenfeld [11] have presented evidence indicating acute myocardial infarction itself may be followed by increased catabolism. Creatinuria, negative nitrogen balance, and increased blood nonprotein nitrogen were found in a study of three patients. If these changes can be reduced as far as possible, it is felt that this would be beneficial to the symptoms of muscular weakness and prostration which patients may manifest when first becoming ambulatory. The transition from bed rest to ambulation of the patients referred to in this program has been unusually smooth. They do not complain of weakness and fatigue to the degree that was formerly noted.

We believe that, in addition to the great psychotherapeutic advantages accruing to such a regimen, there are sound physiological benefits which, combined with the former, have led to much more rapid reconditioning, as well as to increased confidence and understanding on the part of the patient and a much lower incidence of anxiety neurosis. The patient is able to approach resumption of activity after discharge more intelligently and with far less apprehension than ordinarily noted in the absence of such training. It should be remembered that the services of the psychologist, the vocational adviser, and/or social service worker may be necessary for more complete and satisfactory rehabilitation.

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7. Berry, M. R.; Horton, B. T., and MacLean, A. R.: The Importance of Studying Postural Responses of Blood Pressure and Heart Rate with Note on Method of Taking Blood Pressure in Erect Posture, M. Clin. North America **24**:1095, 1940.

8. Miller, E. V.; Michelsen, O.; Benton, W. W., and Keys, A.: Effect of Bedrest on Mineral and Nitrogen Metabolism, Federation Proc. **4**:99, 1945.

9. Deitrick, J. E.; Whedon, G. D.; Shorr, E., and Barr, D. P.: Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing, Transactions of the Ninth Conference, New York, Josiah Macy, Jr., Foundation, 1945, p. 62.

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11. Altschule, M., and Rosenfeld, F.: Increased Catabolism Following Acute Myocardial Infarction, Arch. Int. Med. **80**:74 (July) 1947.

CONCLUSIONS

A program of rehabilitation for patients suffering from acute myocardial infarction is outlined in detail. It involves the coordination of psychotherapeutic and physical and occupational therapeutic activities. It is felt that such a program makes for much better physician-patient relationship, decreases the tendency to anxiety, and prevents general physical deconditioning of the patient. Ambulation is accomplished with less physiological disturbance and apprehension, and strength and endurance are recovered more rapidly. We have been impressed that the incidence of anxiety neurosis following recovery from acute myocardial infarction is much less.

The rehabilitation program contributes to more satisfactory recovery and adjustment on the part of the patient. Whenever possible, patients who should not return to their former type of occupation are seen by the vocational adviser regarding new employment. If the need arises, a social service worker should evaluate the home situation. Both the physician and the patient will have a much clearer concept of the patient's physical and mental capabilities, resulting in more objective and realistic plans for the future.

With an organized program of prescribed progressive physical medicine and rehabilitation activities, there is available to both the physician and the patient a knowledge of the patient's work capacity at the time he is ready to leave the hospital. This capacity for doing a definite amount of work is used as a guide to the type and amount of work activity the patient may wish to pursue upon discharge from the hospital and can be checked periodically.

The personnel of the Medical Service (Cardiac Section) and of the Physical Medicine and Rehabilitation Service, Veterans Administration Hospital, Hines, Ill., cooperated in this program. The Medical Illustration Laboratory supplied the photographs.

HEATSTROKE IN PARKINSONISM

ROBERT E. LITMAN, M.D.
LOS ANGELES

THAT MANY patients with Parkinson's syndrome (paralysis agitans) tolerate extremes of temperature poorly has been recorded previously in the medical literature, but with insufficient emphasis. In 1893 Dana [1] commented upon the unusual sensitivity to heat manifested in Parkinsonism, an observation which was confirmed more recently by Neal.[2] Cases of fatal heatstroke were mentioned briefly in articles by Cooper,[3] Benda and Cobb,[4] and Price and Merritt.[5] The danger of hyperpyrexia occurring as a complication of the treatment of Parkinsonism with atropine-like drugs was stressed by Hall.[6]

Although toxicity due to therapy with belladonna alkaloids undoubtedly increases the incidence of hyperthermia in Parkinsonism, an important predisposing factor frequently is a disturbance of autonomic regulation caused by the underlying pathologic process. Pathologic alterations affecting the hypothalamus [7] and the reticular substance of the brain stem [8] are common in this disease. In my experience,[9] moderate to severe degrees of clinical autonomic dysfunction almost invariably accompany the progressive motor disability of Parkinsonism.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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Three case records of severe heat reactions occurring in ambulatory patients with paralysis agitans are presented below. All these patients showed marked disturbances of autonomic function before the onset of hyperpyrexia.

REPORT OF CASES

CASE 1.—The patient was admitted to the neurology service, June 24, 1948. There was no history of encephalitis or familial degenerative disease. He stated that his symptoms began in 1943, when he was 50 years old, with generalized weakness, back pains, and difficulty in writing. These symptoms gradually progressed. By 1945 there were generalized stiffness of all movements, mild tremor, frequency of urination and incontinence, and dizziness on suddenly assuming the erect position. Results of medical studies, including the basal metabolic rate, were normal. A diagnosis of Parkinsonism was made in 1946, and the patient was given belladonna drops and atropine. During the last year before admission he was bothered by recurrent episodes of oculogyric spasm and by drooling of saliva. He had also been quite constipated and took liquid petrolatum regularly. Sex function had greatly decreased. He did not sweat as much as in former years. The patient said he enjoyed warm weather and liked to lie in the sun, but very hot weather made him listless and feverish.

Physical examination revealed an ambulatory cooperative patient in fairly good general health. The electrocardiogram was normal. The blood pressure was 120/80 in a reclining position. The pulse rate was 70. Results of blood and urine studies were within normal limits. The patient showed a typical Parkinson masked facies. There was a propulsive gait with loss of associated movements. A 5 to 6 per second tremor of the extremities was present. During the examination there were several episodes of spasm of the eyelids. The pupils were unequal but reacted normally. Reflexes were normal to slightly hyperactive bilaterally. The abdominal reflexes were absent. The toe signs were normal. Speech was hardly discernible because of weakness and slurring. An electroencephalogram was normal.

The patient was started on rehabilitation exercises. Treatment was begun with rabellon® (compound of belladonna alkaloids), 5 mg. three times a day. After three days his medication was changed to vinobel® (wine extract of total alkaloids of belladonna root), 1.2 mg. three times a day, because of nausea and vomiting. His hospital course was uneventful until July 3, 1948, when, on the third day of a "heat wave," the patient suddenly displayed fever, lassitude, and weakness. Examination revealed a red, hot, dry skin. His temperature was 103 F., and the pulse was full and pounding, with a rate of 110. His blood pressure was 118/76 reclining and 78/50 sitting. Alcohol sponge baths and cold applications controlled the hyperthermia. The patient was placed in an oxygen tent, where he remained until death. Sweating returned after 72 hours, but the patient never regained control of his body temperature, which fluctuated between 97 and 106 F., according to external conditions. His skin was nearly always cold and moist. Respiratory dysrhythmia, with irregular alternation between apnea and hyperpnea, was frequently observed. The blood pressure and pulse rate were extremely variable. Urinary retention and overflow incontinence developed. Because of laryngeal stridor and pooling of secretions in the pharynx, a tracheotomy was performed on July 15, 1948. Attempts at tube feeding were unsuccessful because of gastric dilatation and regurgitation of fluids into the pharynx.

The patient's course was progressively downward. Repeated episodes of atelectasis occurred, leading to death Sept. 9, 1948. At autopsy there were large areas of demyelination and gliosis in the basal ganglia. Sections through the hypothalamus and midbrain showed tissue destruction.

CASE 2.—This patient, aged 58 years, was admitted to the medical service, July 12, 1948, complaining of generalized weakness, stiffness of gait, incontinence of urine, weak voice, and blackout spells. There was no history suggesting encephalitis. He said his illness began in 1938 with easy fatigability, excessive sweating during hot weather, and nervousness and progressed slowly until 1947, when symptoms of urinary frequency, urgency, and nocturia, together with decreased sexual potency, became severe. The patient had a transurethral prostatic resection in July, 1947, and had unremitting incontinence thereafter.

After the operation, the patient discovered that when he attempted to stand up he became dizzy and would black out. His blood pressure at this time was 140/86 reclining and 85/60

standing. Carotid sinus pressure produced cardiac slowing, a drop in blood pressure, and syncope. Dextrose tolerance tests revealed a mild diabetic curve. Diphenhydramine (benadryl®) hydrochloride medication did not help the patient's condition; it merely increased his tendency toward somnolence.

During the fall of 1947 the patient noted that his voice was weaker. His gait became stiff and uncertain. Although treatment was started with belladonna preparations at this time, the symptoms of weakness, stiffness of gait, fatigability, dizziness on standing, and incontinence of urine did not improve. Examination in July, 1948, revealed an expressionless, mask-like facies, sialorrhea, and a shuffling propulsive gait, with loss of associated movements. There was generalized moderate hyperreflexia with weakness and cogwheel rigidity, with a mild tremor when the patient became excited. He was moderately obese.

Laboratory examination revealed normal blood and urine; a dextrose tolerance test showed a mild diabetic curve with a trace of urinary sugar. The spinal fluid was normal. An electrocardiogram and an electroencephalogram were normal. The basal metabolic rate was —6%. Serologic reactions were negative.

Prolonged observations of the patient's blood pressure and pulse rate revealed a consistent orthostatic hypotension. The blood pressure was in the 130/86 range in the horizontal position. When the patient suddenly stood up, pressure dropped to 50/0, rising gradually over a 2-minute period and stabilizing at approximately 70/40. Despite the changes in blood pressure, the pulse rate was always between 80 and 84. Sudden standing produced no sweating, nausea, or tachycardia. The patient learned to rise to a standing position gradually and thereby avoided attacks of syncope. In the late afternoon his blood pressure would rise to 90/60. Atropine administration did not affect the blood pressure. A sweating test was done in a temperature-controlled room, and the patient was found to perspire freely upon a rise in temperature. Laryngoscopic examination revealed a weakness of the intrinsic muscles, especially on the left. The glottis was considerably narrowed because of abnormal adduction of the vocal cords. Skull and chest roentgenograms were normal. The patient had 200 cc. of residual urine with no signs of cystitis.

The patient was transferred to the neurologic service. He took part in the usual rehabilitation exercises. His medication consisted of rabellon,® 0.5 mg. four times a day, plus dextroamphetamine (dexedrine®) sulfate, 5 mg. two times a day. On Aug. 24, after seven successive days of over 90 F. temperature in Minneapolis, the patient complained of weakness and fever. His temperature was 105 F. His skin was hot and moist. The patient appeared to be in shock. He was given stimulants and put in an oxygen tent. Alcohol sponging lowered his temperature to 101.8 F. Respiration was irregular. During the night 1,000 cc. of saline solution was administered subcutaneously. Fluids given orally were vomited. In the morning the patient was somnolent but not disoriented. He suddenly became cyanotic, and his lungs rapidly filled with fluid. Bronchoscopy revealed a great amount of thin, watery secretion in the trachea and bronchi. This was aspirated. Shortly thereafter the patient stopped breathing. Artificial respiration and stimulants were ineffective. Postmortem examination revealed marked pulmonary edema. Serial sections of the brain stem and hypothalamus were made, but by accident the tissues were destroyed during processing.

Case 3.—This patient, aged 50, was admitted to the neurological service, Sept. 9, 1948. He stated that he had been well until the summer of 1945, when, at the age of 47 years, he first had urinary frequency and stress incontinence. His past history was normal in that there had been the usual childhood illnesses but no episodes of high fever or disorientation and nothing suggestive of encephalitis. At the age of 32 he had had an uneventful thyroidectomy. There was no family history of neurological disorder. He had served in the Armed Forces in 1918-1919 and again in 1942-1943.

The patient underwent a transurethral resection in November, 1945. Incontinence followed this procedure, and from then on the patient wore a penile clamp. During the summer of 1946 he complained of weakness and blackout spells, which occurred upon his assuming erect posture. A medical consultant noted the presence of tremor and slightly slurred speech.

The patient was admitted to the medical service Aug. 1, 1947, because of syncope. Results on an examination of spinal fluid, the basal metabolic rate, an electrocardiogram, and an electroencephalogram were normal. It was found that the patient's blood pressure was 140/90 reclining, but that when he stood the pressure fell to 50/0. His pulse rate of 78 did not change. During the

hot weather in August the patient's temperature varied from 101 to 104 F., with tachycardia, a pulse rate of 100 to 120. No infectious source could be located, but it was noted that sweating was deficient. Members of the medical staff felt that the fever was due to the environmental heat and lack of sweating. Neurological consultants noted fixed pupils, nystagmus to the right, increased deep reflexes, absent abdominal reflexes, and a mild tremor. No definite neurological diagnosis could be made. With the coming of cooler weather, the patient's condition improved remarkably, and he was discharged in November. He was not given atropine-like drugs.

The patient returned on Sept. 9, 1948. This time he was rushed to the neurological service as an emergency admission. During the hot weather of August, 1948, there had been hyperthermia, weakness, and a rapid deterioration in his general physical condition. There was marked weakness of speech; swallowing was difficult. There was considerable rigidity of the muscles with mild tremor. The patient was unable to get out of bed because of severe orthostatic hypotension. It was felt that the diagnosis was Parkinsonism. A test on Sept. 14 showed almost no sweating. The patient complained of severe weakness and discomfort during the period of exposure to heat. His blood pressure was 130/80 reclining and 70/40 standing. The patient now had auricular fibrillation. Circulation time and venous pressure were normal. The electroencephalogram was normal. The basal metabolic rate was —15%.

He was given bellabulgara® (extract of Bulgarian belladonna root), with no great improvement. The nurse reported that at night respiration was quite irregular. The patient continued to complain of weakness and syncope, but he became ambulatory on the rehabilitation program and made good improvement in self-care. Plans were made for his discharge. The patient died unexpectedly in the early hours of the morning on April 19, 1949. The cause of death was listed as respiratory failure. Autopsy was not permitted.

COMMENT

In these patients numerous signs and symptoms of many years' duration suggested involvement of the autonomic nervous system. The earliest complaints were weakness and excessive fatigue aggravated by hot weather. Symptoms of constipation, impotence, and urinary bladder disturbances were prominent, suggesting a considerable derangement of visceral autonomic functions. There was carotid sinus hypersensitivity in Patient 2. Sweating was decreased in Patients 1 and 3. A striking feature was dizziness and syncope on standing. Patients 2 and 3 were investigated thoroughly, and they consistently showed a severe orthostatic hypotension.

The syndrome of orthostatic hypotension has been described in detail.[10] Essentially, there is a failure of vasoconstriction and cardiac acceleration, which mechanisms normally compensate for the pooling of blood in the lower extremities due to gravity on standing. Frequently there are associated disturbances of sweating and other autonomic functions. In severe cases other signs of neurological disease usually occur. It is assumed that the pathologic processes involve the hypothalamus or its descending tracts in the midbrain. Two cases of orthostatic hypotension associated with Parkinsonism have been reported.[11] It is interesting that one of the

10. (*a*) Bradbury, S., and Eggleston, C.: Postural Hypotension, Am. Heart J. **1**:73, 1925. (*b*) Ellis, L. B., and Haynes, F. W.: Postural Hypotension, with Particular Reference to Its Occurrence in Disease of the Central Nervous System, Arch. Int. Med. **58**:773 (Nov.) 1936. (*c*) Stead, E. A., and Ebert, R. V.: Postural Hypotension: A Disease of the Sympathetic Nervous System, ibid. **67**:546 (March) 1941.

11. Young, R. H.: Association of Postural Hypotension with Sympathetic Nervous System Dysfunction: Case Report, with Review of Neurologic Features Associated with Postural Hypotension, Ann. Int. Med. **15**:910, 1941. Nylin, G., and Levander, M.: Studies of the Circulation with Aid of Tagged Erythrocytes in Case of Orthostatic Hypotension (Asympathicotonic Hypotension), ibid. **30**:723, 1948.

three original patients with orthostatic hypotension described by Bradbury and Eggleston is reported to have died unexpectedly during a summer "heat wave."[10a]

The principal mechanisms for heat dissipation in human beings are sweating and peripheral vasodilatation (with compensatory central vasoconstriction). If these mechanisms are impaired, the body cannot adjust to prolonged external heat. Collapse and hyperthermia result. Ferris and co-authors [12] found that in classic cases of heatstroke the sudden hyperpyrexia is preceded by an abrupt cessation of sweating. It is as if an acute failure of the overtaxed "sweating center" occurred. Case 1 is a typical example. If impairment in circulatory adaptation to heat predominates, there develops first a state of vasomotor collapse, followed by hyperthermia, as in Case 2. In Case 3 the autonomic decompensation was less acute and not quite so overwhelming. In all cases hyperpyrexia resulted in a violent exacerbation of the previous autonomic derangement, and symptoms of damage to the respiratory mechanisms became prominent. The eventual mode of death was that of respiratory failure.

I agree with Neal [2] that the treatment of Parkinsonism with artificial fever, as sometimes has been recommended in the past, should be discouraged. Hyperpyrexia has proved of no benefit in Parkinsonism, and at least a dozen fatalities have been reported.[13]

These case histories provide only suggestive evidence concerning the possible deleterious effects of drug therapy. In Patients 1 and 2, who were taking belladonna alkaloids, the initial hyperpyrexia proved fatal. During periods when he was receiving no antispasmodic medicament, Patient 3 survived two episodes of hyperthermia, only to die unexpectedly at the time he was taking a belladonna preparation and apparently responding favorably. It seems probable that belladonna drugs, which tend to inhibit sweating, increase sensitivity to heat.

It is apparent that elevated environmental temperatures may be exceedingly dangerous for patients undergoing active treatment for Parkinsonism. In many cities of the United States this is a problem of considerable importance, particularly to a physician who has an appreciable number of patients with Parkinsonism under his care during the summer, for example, on a continuous rehabilitation program.

The following measures were carried out successfully in the rehabilitation service of the Veterans Administration Hospital, Minneapolis, in 1949 and 1950 and are recommended for general application. During the hot weather, activities were reduced and physical exertion, especially outdoors, was discouraged. Clothing was light, and rest periods were frequent. Ingestion of fluids was encouraged by making cold drinks, fruit juice, and water easily available. Supplementary salt tablets were given only on order of the resident. Rounds were conducted once a day by the physician in charge and twice a day by the nurse to determine presence of sweating. Reports of lassitude, anorexia, nocturia, and dry skin were immediately investigated.

It was possible to equip one five-bed room with an air-conditioning device. Patients with Parkinsonism starting new medication in hot weather always slept

12. Ferris, E. B.; Blankenhorn, M. A.; Robinson, H. W., and Cullen, G.: Heat Stroke: Clinical and Chemical Observations on 44 Cases, J. Clin. Invest. **17**:249, 1938.

13. Carpenter, C. M., and Warren, S. L.: Artificially Induced Fever in the Treatment of Disease, New York J. Med. **32**:997, 1932. Von Witzleben, H. D.: Methods of Treatment in Post-Encephalitic Parkinsonism, New York, Grune & Stratton, Inc., 1942.

in this room; other patients were transferred to it as soon as indications of heat intolerance were observed. With this program there were no severe heat reactions and no fatalities.

SUMMARY

Hyperthermic reactions may dangerously complicate the treatment of patients with Parkinsonism during hot weather. In certain cases impairment of the autonomic circulatory and sweating mechanisms causes increased sensitivity to heat. This heat sensitivity is augmented by therapy with atropine-like drugs. A prophylactic hot-weather regimen for hospitalized patients is outlined.

BENIGN BUNDLE BRANCH BLOCK

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THE LOCALIZATION of block in the main branches of the bundle of His was clarified by the studies of Wilson and his co-workers.[1] In this regard precordial electrocardiography proved to be of great value. The clinical significance of these findings, however, has been confusing, and it is well known that right or left bundle branch block is commonly associated with coronary artery disease. Bundle branch block may also occur in valvular disease, particularly with aortic stenosis. Furthermore, some evidence has appeared to indicate that right bundle branch block in general may indicate a better prognosis than left bundle branch block.[2] Recently, it has been observed that right bundle branch block, complete or incomplete, is a common finding in patients with congenital cardiac disorders, especially those with atrial septal defects.[3] It is the main purpose of this study to call attention to a group of patients who have bundle branch block (mainly right) and who present no other evidence of organic heart disease. This condition we term

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1. Wilson, F. N.; Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle Branch Block, Am. Heart J. **7**:305, 1932. Wilson, F. N.; Johnston, F. D.; Hill, I. G. W.; Macleod, A. G., and Barker, P. S.: The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S Deflections in Lead I, ibid. **9**:459, 1934. Wilson, F. N.; Johnston, F. D., and Barker, P. S.: Electrocardiograms of an Unusual Type in Right Bundle Branch Block, ibid. **9**:472, 1934. Wilson, F. N.: Concerning the Form of the QRS Deflections of the Electrocardiogram in Bundle Branch Block, J. Mt. Sinai Hosp. **8**:1110, 1942. Wilson, F. N.; Johnston, F. D.; Rosenbaum, F. F.; Erlanger, H.; Kossman, C. E.; Hecht, H.; Cotrim, N.; Menezes de Oliveira, R.; Scarsi, R., and Parker, P. S.: The Precordial Electrocardiogram, Am. Heart J. **27**:19, 1944.

2. Willius, F. A.; Dry, T. J., and Reeser, R., Jr.: Life Expectancy in Conductive Disturbances Affecting the Ventricular Complex of the Electrocardiogram: I. General Considerations of Bundle Branch Block with Concordant and with Discordant Graphs and the Wide S Wave Pattern, Based on 1,611 Cases, Arch. Int. Med. **67**:1008 (May) 1941. Perera, G. A.; Levine, S. A., and Erlanger, H.: Prognosis of Right Bundle Branch Block: A Study of 104 Cases, Brit. Heart J. **4**:35, 1942. Messer, A. L.; Birmingham, A.; Johnson, R. P.; Shreenivas, and White, P. D.: Prognosis in Bundle Branch Block: III. A Comparison of Right and Left Bundle Branch Block with a Note on the Relative Incidence of Each, Am. Heart J. **41**:239, 1951. Levine, S. A.: Clinical Heart Disease, Ed. 4, Philadelphia, W. B. Saunders Company, 1951.

3. Barber, J. M.; Magidson, O., and Wood, P.: Atrial Septal Defect, Brit. Heart J. **12**:277, 1950. Nadas, A.: Personal communication to the authors.

benign bundle branch block. Wolfram [4] reported 52 instances of bundle branch block from a study of 5,000 routine tracings in the Cardiac Clinic, Veterans Administration Regional Office, Dallas, Texas. Of these, 35 were of right and 17 were of left bundle branch block. Twenty-six of the former cases and seven of the latter had no other evidence of heart disease. However, there were no follow-up studies to determine how benign these cases might prove to be.

It is not intended to take up other aspects of the problem of bundle branch block except to reemphasize the fact that this condition, even when coupled with organic heart disease, is compatible with a long duration of life, and that among cases of organic heart disease block of the right branch seems to have a better prognosis than left block.

MATERIAL OF STUDY

Inasmuch as the study of cases observed in a hospital, particularly one with many public-ward beds, is weighted by the incidence of critically sick patients and does not afford an opportunity to appraise the general prognosis of the problem involved, our cases were selected from the office practice of one of us. There were 452 instances of bundle branch block observed from 1922 to 1951. Those patients who showed complete heart block or intermittent, indeterminate, or incomplete bundle branch block were omitted from this study. Also, patients with paroxysmal tachycardia of the ventricle and Wolff-Parkinson-White syndrome were excluded. The classification of right and left bundle branch block was made according to the teachings of Wilson.

BENIGN BUNDLE BRANCH BLOCK

During the past few decades, we were impressed with the fact that now and again patients both in hospital and particularly in ambulatory practice were observed to have bundle branch block essentially as an accidental finding. They showed no other subjective or objective evidence of heart disease. In such patients there was no cardiac enlargement on physical examination or roentgenograms, no hypertension or murmurs, no past history of rheumatic fever, no evidence of congenital heart disease, and no stigmata of coronary artery disease. They could carry on normal activities without chest distress or dyspnea. In fact, the abnormal electrocardiograms were generally obtained on a routine check-up or on an insurance examination. In the latter case the patients would be denied the policy, after which they would make a tour of physicians and heart specialists. In the course of time the number of such cases increased, so that, whereas formerly encountering one of them was a rare experience, more recently it has become not uncommon. Almost invariably, when the abnormal electrocardiogram was detected the patient was labeled as having serious heart disease, was generally thought to be suffering from coronary artery disease, and was instructed to restrict activities and carry out the many precautions that are customarily employed in the care of serious heart disease. The fallacy of such admonitions and diagnostic inferences became apparent when the patients were observed to carry on well and normally year after year, some even for 20 years, without any restriction in their activities and showing no objective evidence of heart disease except the constant presence of bundle branch block.

Among the entire series of 452 patients with both right and left bundle branch block, we found 80 who belonged to this group. From among these 80 patients all those were excluded who had a follow-up study of less than five years. These

4. Wolfram, J.: Bundle Branch Block Without Significant Heart Disease, Am. Heart J. **41**:656, 1951.

numbered 50 patients, so that 31 remained whom we grouped as having benign bundle branch block (Table 1). As was stated above, these 31 persons had no subjective or objective evidence of heart disease. They were observed for varying periods of 5 to 29 years, and at no time did they display cardiac abnormalities that threw any light on the original cause of the abnormal electrocardiogram. Only 6 of these 31 are known to have died, 3 of unknown causes, 1 of brain tumor, 1 of carcinoma of the prostate, and the last suddenly of a coronary attack. The last patient died at the age of 63, 20 years after right bundle branch block was first observed and three years after the first evidence of angina appeared. In other words, he had

TABLE 1.—*Benign Bundle Branch Block*

Type of Bundle Branch Block	No. of Cases	Age, Yr.*	Sex	Duration of Bundle Branch Block, Yr.†
Right	27	Range, 8 to 70 Average, 48.8	M, 20 F, 7	Range, 5 to 29 Average, 12.2
Left	4	Range, 43 to 71 Average, 57.8	M, 1 F, 3	Range, 7 to 12 Average, 10
Total	31	Average, 50	M, 21 F, 10	Average, 11.9

* Age when bundle branch block was first observed.

† Since all but six are still alive and well, these figures indicate only the period of observation and not the length of life with bundle branch block.

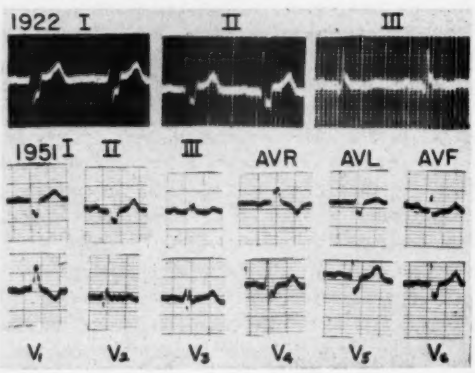

Fig. 1.—Electrocardiograms of W. W., first seen at the age of 8 years because of questionable rheumatic fever on Oct. 10, 1922. Upper tracing (Nov. 3, 1922) shows right bundle branch block. He has shown no signs or symptoms of heart disease and does hard physical work. Lower tracing (Aug. 2, 1951) shows same right bundle branch block.

benign, symptomless bundle branch block for 17 years before any cardiac disability developed. There were 27 patients with right and 4 with left bundle branch block among these 31 benign cases. The average duration from the first detection of bundle branch block was 11.9 years, and the range was 5 to 29 years. The longest case was that of a boy who was first seen at the age of 8 years. At that time (1922), a few months after an illness that may have been atypical rheumatic fever, electrocardiograms were characteristic of right bundle branch block. He was followed all these years and has never shown any other evidence of cardiac involvement. He

has been in perfect physical condition, has been able to do strenuous work, and, even when last seen in August, 1951, showed no cardiac enlargement, hypertension, or murmurs. His electrocardiograms have remained essentially unchanged for the past 29 years (Fig. 1).

Inasmuch as it is quite certain that most of these patients were alive and well for a considerable time after they were last heard from, the average figure of 11.9 years is an understatement, especially since a fair number who were last heard from as long ago as 1940 to 1945 could not be traced. There were 21 males and 10 females, roughly a ratio of 2:1. The age of these patients when the block was first noted ranged from 8 to 71 years (average, 50 years). It is apparent from the above that right bundle branch block is much commoner than left block and that males predominate in this group.

CORONARY ARTERY DISEASE AND BUNDLE BRANCH BLOCK

The second point that interested us in this study was the difference between right and left bundle branch block when they were associated with coronary artery disease. Of the entire series of 452 patients showing either type of bundle branch

TABLE 2.—*Fatal Cases of Bundle Branch Block with Coronary Artery Disease* *

Type of Bundle Branch Block	No. of Cases	Sex	Age at Onset of Bundle Branch Block, Yr.	Duration of Coronary Artery Disease, Yr.	Duration of Bundle Branch Block, Yr.
Right.....	22	M, 19	Range, 35 to 74	Range, 2 to 22	Range, 4/12 to 21
		F, 3	Average, 55.9	Average, 8.6	Average, 6.7
Left.....	40	M, 27	Range, 42 to 73	Range, 4/12 to 25	Range, 1/12 to 25
		F, 13	Average, 50.7	Average, 5.6	Average, 3
Total.....	62	M, 46	Average, 52.5	Average, 6.7	Average, 4.3
		F, 16			

* Patients who had bundle branch block of less than one month's duration were omitted.

block with varied causations, there were 132, or 28.3%, who were known to have died. Among these fatal cases, 62, or about one-half, were definite instances of either angina pectoris or coronary occlusion. No doubt, some of the other patients may also have had coronary artery disease. Because we have been gaining the impression that even when bundle branch block is associated with coronary artery disease the prognosis appears to be somewhat better when the right branch is involved rather than the left, the duration of life after the onset of block was determined in these fatal cases (Table 2). This ranged from four months to 21 years in right bundle branch block (average, 6.7 years) and one month to 25 years in left bundle branch block (average, 3 years). Similarly, the average duration of life from the onset of coronary artery disease to death was 8.6 years (range, 2 to 22 years) for those with right bundle branch block and 5.6 years (range, 4 months to 25 years) for those who had left bundle branch block. It seems significant that the length of life in patients with coronary disease was three years longer when right bundle branch block was present, despite the fact that the average age at onset of the disease was five years older (55.9 years) than with left bundle branch block (50.7 years).

Males predominate in this group as they do in other types of coronary disease. Among the 62 patients who died, there were 46 males and 16 females (ratio of

3:1). More impressive is the fact that among those with right bundle branch block the proportion of males to females was about 6:1. The clinical impression seems to be confirmed that the prognosis of right bundle branch block when associated with coronary artery disease is definitely better than that of left bundle branch block with coronary disease.

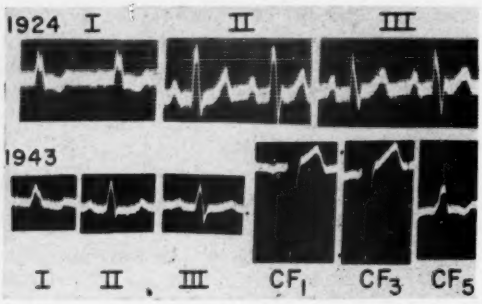

Fig. 2.—Electrocardiograms of H. L., who was aged 60 when first seen. Upper tracing (Dec. 3, 1924) shows left bundle branch block when he had no cardiac symptoms or abnormal signs. Angina began in January, 1931; patient remained ambulatory and did well till 1947 and then displayed signs of congestive failure. He died in December, 1949, at the age of 85 years. Lower tracing shows same left bundle branch block which he had had for at least 25 years.

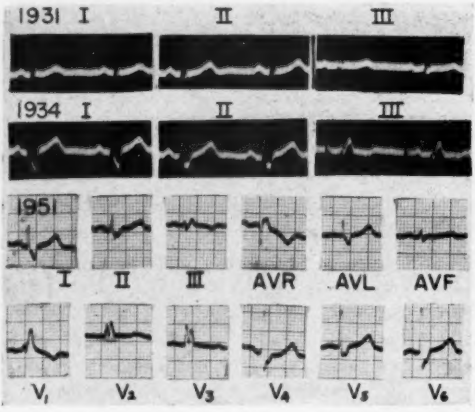

Fig. 3.—Electrocardiograms of P. L., a man 71 years old, who had definite angina pectoris for last 22 years. Upper tracing (March 26, 1931) shows normal curves. Middle tracing (April 2, 1934) shows right bundle branch block. Lower tracing (May 22, 1951) shows the same right bundle branch block. Patient is ambulatory and doing well.

The final point we wish to emphasize is the fact that even when bundle branch block is present in patients suffering from coronary artery disease the condition is compatible with a long and useful life. The electrocardiograms of two patients shown in Figures 2 and 3 are striking illustrations of this fact. One of these two (Fig. 2) was seen at the age of 60, when he had left bundle branch block but was otherwise well. Seven years later angina pectoris first developed, and he carried

on comfortably until he was 84 years old. He then had congestive symptoms and died one year later, 25 years after first showing the abnormal tracing. The second case (Fig. 3) was that of a man who was first seen at the age of 49 years. He had displayed classic mild symptoms of angina a few months before. The electrocardiogram at this time was normal. In 1934 he first showed right bundle branch block and has had identical curves ever since. Twenty years after the onset of his symptoms and 17 years after the first appearance of abnormal electrocardiograms, he is still ambulatory, enjoying good health and taking only an occasional glyceryl trinitrate tablet. These patients may be somewhat exceptional, but we have seen a good number of similar patients carrying on satisfactorily for more than 10 years.

COMMENT

Clinical data have been presented to indicate that there is an appreciable group of persons who show bundle branch block, generally involving the right branch, with no other evidence, subjective or objective, of cardiac disease. In fact, these patients appear to be well. The cause of the abnormal electrocardiograms is obscure. It may well be that in some instances the bundle branch block was present for years before it was first accidentally discovered, or was present even at birth. Although bundle branch block is common with congenital atrial septal defects, the absence of cyanosis, cardiac enlargement, heart murmurs, or abnormal configuration of the heart on roentgen examination fairly well rules out this possibility in the group of patients studied here. The final explanation that may be offered is that the conduction defects are the result of otherwise apparently benign viral or bacterial infections.[5] It is well known that diphtheria can cause atrioventricular heart block, but in the past when this complication occurred with diphtheria it was generally, but not always, fatal. There is some indirect evidence that ordinary Adams-Stokes disease may be a late aftermath of early severe diphtheria.[6] It has also been observed in recent years that a variety of infections, apart from rheumatic fever, which otherwise run a benign course may occasionally show transient first-degree heart block.

One is, therefore, tempted to assume that the patients with benign bundle branch block in this study, who gave no evidence of coronary artery disease or other disease of the heart muscle, acquired the block during some benign infection that did little or no harm to the heart. If, therefore, bundle branch block is detected in a patient who shows no other evidence of disease, the physician should not look upon his condition as grave. Too often this finding becomes synonymous with coronary artery disease. It is wiser to allow such persons to carry on essentially normal duties, even if on rare occasions graver evidence of heart disease, such as atrioventricular block or angina pectoris, becomes evident. Finally, this study affords evidence that when organic heart disease, particularly coronary artery dis-

5. Pearce, J. M., and Levine, H. D.: The Anatomic Cause of Electrocardiographic Changes in Virus Myocarditis of Rabbits, Am. Heart J. **25**:102, 1943. Rosenberg, D. H.: Electrocardiographic Changes in Epidemic Parotitis (Mumps), Proc. Soc. Exper. Biol. & Med. **58**:9, 1945. Paul, W. D.; Rhomberg, C., and Cole, J.: Transitory A-V Block Occurring During Scarlet Fever, Am. Heart J. **31**:138, 1946. Goldfinger, D.; Schreiber, W., and Wosika, P. H.: Permanent Heart Block Following German Measles, Am. J. Med. **2**:320, 1947.

6. Butler, S., and Levine, S. A.: Diphtheria as a Cause of Late Heart-Block, Am. Heart J. **5**:592, 1930.

ease, is present and is associated with bundle branch block, those with right bundle branch block have a decidedly better prognosis than those with left blocks. There is also a significant number of patients with right or left bundle branch block and coronary artery disease who carry on very well for many years. They live comfortably for 10 to 25 years with this combination, so that the physician should not necessarily give a poor prognosis in these circumstances.

SUMMARY

Thirty-one instances of benign bundle branch block were found in a consecutive series of 452 cases of bundle branch block (left or right) observed in office practice during the years 1922 to 1951. The benign group had no other subjective or objective evidence of heart disease. They have been followed for many years (5 to 29 years) and have remained well. The cause of the block is obscure. We suspect such patients may have acquired the electrocardiographic abnormality as a result of some intercurrent, otherwise harmless infection which left no other injury to the heart. The physician should make light of this condition and permit such patients to carry on normal duties.

In a study of 62 patients with death from coronary artery disease who also had bundle branch block, it was found that those with right bundle branch block lived three or more years longer than those with left block, after the onset of either cardiac symptoms or bundle branch block. There were numerous patients having coronary artery disease with bundle branch block who carried on satisfactorily for 10 to 25 years after the abnormal electrocardiograms were first detected. The inference is that the prognosis need not be grave in these circumstances.

LEPTOSPIRAL MENINGITIS

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A CONSIDERABLE amount of new information concerning leptospiral infections has been gained recently, principally through work done in Europe and Australia. Laboratory investigations have led to the identification of new strains; epidemiologic observations have thrown light on the natural reservoirs of infection, and clinicians have described several different expressions of leptospiral infection in man. In America, there seems to have been a curious lack of interest in this kind of infection. Only three strains of the parasite (Leptospira icterohemorrhagiae, Leptospira canicola, and Leptospira pomona) have been identified here. Although cases of Weil's disease (spirochetal jaundice) have been recognized in various parts of the country, there is reason to believe that the incidence of leptospiral infection is probably much higher than is appreciated, particularly with respect to the less spectacular clinical patterns.

In a previous article we reported briefly the observation of two cases of leptospiral meningitis in Atlanta, together with the finding of serologic evidence of leptospiral infection in nine other patients with "benign aseptic meningitis" observed elsewhere.[1] The present article deals with an extension of that work.

BACTERIOLOGIC ASPECTS

Leptospirae belong to the Order Spirochaetales. They are delicate, tightly coiled organisms, usually hooked at one or both ends. When observed by dark-field microscope, they exhibit two types of motility: whirling on the long axis and fairly rapid forward or backward motion. Leptospirae can be maintained in the laboratory by culture in media containing serum or other body fluid. Satisfactory methods of storing living organisms have not yet been devised, it being necessary to subculture stock strains every 10 to 15 days. The pathogenicity for common laboratory animals is variable; some use of this variability is made in identification of newly isolated strains. The principal means of differentiating strains, however, is by serologic reactions, an agglutination technique usually being used.

Pathogenic leptospirae have been recognized in every continent. About 30 serologic strains have been described, most of them in Asia and the East Indies. In

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From the Medical Service, Grady Memorial Hospital, and the Department of Medicine, Emory University School of Medicine.

1. Beeson, P. B., and Hankey, D. D.: "Benign Aseptic Meningitis" as a Manifestation of Leptospiral Infection, Tr. A. Am. Physicians **63**:130, 1950.

addition, a number of saprophytic strains have been found, usually in stagnant water and pools.

The epidemiology of the leptospiroses involves many wild and domestic animals, including rats, mice, dogs, foxes, swine, cattle, and horses. Infection is usually conveyed to human beings via the urine of these animals, indirectly, through contamination of standing water in pools, on fields, or on floors. There is a prominent occupational factor in infection: Particularly hazardous are farming, rice or cane cutting, dairying, coal mining, sewer work, poultry dressing, and fish cutting. As a consequence of the occupational factor, the leptospiroses occur most frequently in males above the age of 15 years. It is thought that the usual portal of entry for infection is through cuts and abrasions in the skin, a route which has been proved possible in experimental animals. Swimming or accidental immersion in stagnant pools has also appeared to be responsible for infection in many cases. Possibly the portal of entry here is the conjunctiva or nasal mucous membrane.

The organisms are rapidly destroyed in acid medium, and for that reason it is thought that few infections are acquired through the gastrointestinal tract. They do not survive long in cold temperatures; this perhaps contributes to the fact that human infections occur most frequently in summer.

CLINICAL MANIFESTATIONS

The various clinical manifestations of leptospiral infection can be classified under the icteric and anicteric forms. The icteric form (Weil's disease) is the severest. It is most usually caused by the Lept. icterohemorrhagiae strain, although other strains can produce the picture. The clinical features of Weil's disease are distinctive. There is a sudden onset with fever, chills, severe muscle pain, and conjunctival effusion. Fever usually subsides at about the fifth day, but at that time signs of hepatitis and nephritis may appear—enlarged and tender liver, jaundice, oliguria, albuminuria, hematuria, and azotemia. The blood leucocyte count is elevated, and there is pleocytosis in the spinal fluid in about 90% of cases.[2] Physical signs of meningitis may be present. In a few cases there are signs only of nephritis, without evidence of hepatitis or meningitis; here an erroneous diagnosis of acute glomerulonephritis may be made.[3] The anicteric leptospiroses are known by a variety of terms, including "cane fever," "swamp fever," "rice field fever," and "swineherd's disease." They are mild grippe-like illnesses, lasting only a few days; some have a diphasic course, two febrile periods separated by a day or two of normal temperature. Signs of meningitis are common, and this form of leptospiral infection can easily be mistaken for other causes of "benign aseptic meningitis," such as mumps, poliomyelitis, and lymphocytic choriomeningitis. The strains most frequently identified with the anicteric variety are Lept. pomona, Leptospira mitis, and Leptospira grippotyphosa. The strain commonly carried by dogs, Lept. canicola, can produce the picture of Weil's disease in man occasionally, but in most instances it causes a short febrile illness, with or without signs of meningitis.

2. Cargill, W. H., Jr., and Beeson, P. B.: The Value of Spinal Fluid Examination as a Diagnostic Procedure in Weil's Disease, Ann. Int. Med. **27**:396, 1947.

3. Stiles, W. W.; Goldstein, J. D., and McCann, W. S.: Leptospiral Nephritis, J. A. M. A. **131**:1271 (Aug. 17) 1946.

PLAN AND METHODS OF PRESENT STUDY

During a two-year period, beginning in October, 1949, a systematic search for evidence of leptospiral infection was made on all patients admitted to Grady Hospital with the clinical picture of "benign aseptic meningitis." Diagnostic procedures employed included cultures, agglutination tests, animal inoculations, and direct examination of body fluids by dark-field microscope.

Culture Medium.—The culture medium used was Korthof's[4]; it was dispensed in 15-cc. screw-capped test tubes in 2-cc. quantities. The size of the inoculum was usually one loopful of another culture or one drop of a body fluid. Cultures were incubated at 27 C. and were examined microscopically for growth at weekly intervals for three weeks after inoculation. Stock cultures for the agglutination tests were transferred at 10-day intervals.

Agglutination Test.—The agglutination test was carried out by using living culture, 7 to 10 days old, as antigen. Serial dilutions of serum were thoroughly mixed with equal quantities of antigen on glass slides and sealed under cover slips with petroleum jelly. Antigen control preparations were made in the same way with saline solution and culture. After standing at room temperature for two hours, the preparations were examined by low-power objective of a dark-field microscope. The degree of agglutination was graded 1+ to 4+, the term 4+ being applied to reactions in which all organisms appeared to be agglutinated in tight "balls." The 1+ reading was assigned to reactions in which there was definite aggregation of some leptospirae, many of the organisms remaining discrete. Intermediate stages of agglutination were graded 2+ or 3+. Although lysis was sometimes seen in these preparations, it was not found to be useful as a criterion in determining the serologic titer. The end-point used in expressing the titer was 2+ or greater. The following strains were employed: Lept. icterohemorrhagiae, Lept. pomona, Lept. canicola, Leptospira ballum, Lept. grippotyphosa, Leptospira hebdomadis-T, Leptospira saxkoebing, and Lept. mitis. As a screening method, convalescent serum was tested against each antigen in a dilution of 1:200. In the event of a positive reaction, all serums from the patient were titered in twofold dilutions, beginning at 1:200. It is generally agreed that a serologic titer of 1:300 or higher is diagnostic of leptospiral infection.[5]

Animal Inoculations.—In the animal inoculations hamsters were employed. Young animals weighing less than 25 gm. were found to be most suitable. They were inoculated intraperitoneally with 1 cc. of the body fluid. When urine was to be tested, it was brought to the laboratory immediately and centrifuged at 2,000 rpm for 20 minutes, and the sediment from 50 cc. was inoculated. Two or more animals were used for each test. At the end of five days, or earlier if it appeared listless, the animal was killed, the heart blood was cultured, and an emulsion was made of the kidneys, using Korthof's medium as the suspending fluid. This was then inoculated into two more young hamsters. Frequently it was necessary to pass such tissue emulsions at five-day intervals through four or five successions of animals before leptospirae could be demonstrated; then they could also be recovered easily by culture of the kidney and the heart blood and could sometimes be seen on direct examination of the animal's blood. There was never any evidence of naturally occurring leptospiral infection in the colony of hamsters used.

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4. Korthof's medium is made as follows:

Buffer:	Solution, %	Amount, Cc.
NaCl	2.5	11.2
$NaHCO_3$	0.1	4.0
KCl	0.1	8.0
$CaCl_2$	0.1	8.0
KH_2PO_4	2.5	1.44
Na_2HPO_4	2.5	7.68
		40.32

Dilute above quantity of buffer to 200 cc. with distilled water. Adjust pH to 7.4. Autoclave at 15 lb. (6.8 kg.) for 20 minutes. Centrifuge or filter out precipitate. To 8 parts buffer, add 1 part 1% tryptose broth, sterile, at pH 7.4. Resterilize. Check sterility. To the 8 parts buffer and 1 part 1% tryptose broth, add 1 part sterile rabbit serum.

5. Bertucci, E. A., Jr.: Leptospirosis, Am. J. M. Sc. **209**:86, 1945.

Examinations of Body Fluids.—Many examinations of body fluids were carried out on patients suspected of leptospiral infection. We have not yet succeeded in finding leptospirae by dark-field examination of a patient's blood, either in Weil's disease or in leptospiral meningitis; consequently, we do not recommend this procedure for routine work. Similarly, the organisms have never been observed by us in spinal fluid. We have found them on direct examination of urine during the third week of illness in one patient with leptospiral meningitis and in one patient with Weil's disease. We have also isolated them from the urine by animal inoculation and by culture in one of four cases of leptospiral meningitis and in four of seven cases of Weil's disease. Blood culture was positive in 2 of 10 cases of Weil's disease and 1 of 4 cases of leptospiral meningitis; spinal fluid culture was positive in 1 of 7 cases of Weil's disease.

In addition to studies on cases of leptospiral meningitis in our own clinical material, agglutination tests were carried out on serums of patients from other localities who had been suspected of having neurotropic virus infection. These were obtained from a number of other laboratories where viral diagnostic studies are carried out.[6]

RESULTS

During the two-year period of the study, six cases of leptospiral meningitis were observed at Grady Hospital, Atlanta. We also had opportunity to follow the course of a seventh case at Lawson Veterans Administration Hospital, Atlanta.

In addition to the cases which came under our personal observation, serologic evidence of acute leptospiral infection was obtained in 17 of approximately 500 pairs of serums obtained from other laboratories. These serums were supposedly from patients in whom neurotropic virus infection was suspected. It should be pointed out, however, that many of them had been collected during epidemics of poliomyelitis, mumps, and encephalitis, so that the incidence of leptospiral infection in this group probably does not represent its true frequency among sporadic cases of "benign aseptic meningitis." Of possibly greater significance is the proportion of positive results in our own hospital, where 6 cases of leptospirosis were found among 35 patients with aseptic meningitis.

Geographic Distribution.—The geographic distribution of the cases described in this report is not a reliable index of the distribution of leptospiral meningitis in the United States because many of the specimens happened to be obtained from laboratories in the southern part of the country. Evidence of leptospiral infection was obtained in residents of the following states: Georgia, Alabama, Louisiana, Texas,

6. The following physicians supplied serums for these tests: Dr. Morris Schaeffer, Virus Research Laboratory, Communicable Disease Center, United States Public Health Service, Montgomery, Ala.; Dr. Lewis Thomas, Department of Medicine, Tulane University Medical School, New Orleans; Dr. S. Edward Sulkin, Department of Bacteriology, Southwestern Medical School, Dallas, Texas; Dr. M. Michael Sigel, Virus Diagnostic Service, Children's Hospital of Philadelphia, Philadelphia; Dr. William S. Jordan, Department of Preventive Medicine, Western Reserve University, Cleveland; Dr. William McD. Hammon, Graduate School of Public Health, University of Pittsburgh, Pittsburgh; Dr. Edward C. Curnen Jr., Department of Pediatrics, Yale University Medical School, New Haven, Conn.; Dr. Morton Hamburger, Department of Medicine, University of Cincinnati Medical College, Cincinnati; Dr. Joseph E. Smadel, Department of Virus and Rickettsial Diseases, Army Medical Department Research and Graduate School, Washington, D. C.; Dr. George S. Mirick, Johns Hopkins Hospital, Baltimore; Dr. Edwin H. Lennette, Viral and Rickettsial Disease Laboratory, California State Department of Public Health, Berkeley, Calif.; Dr. Albert Milzer, Bacteriology and Virology Department, Michael Reese Hospital, Chicago; Dr. William A. Knight, St. Louis City Hospital, St. Louis, and Dr. Albert B. Sabin, Children's Hospital Research Foundation, Cincinnati.

California, Ohio, and Connecticut. Since leptospirosis has been demonstrated in rats [7] and dogs [8] throughout the United States, there is reason to believe that human leptospirosis can occur everywhere; indeed, cases of Weil's disease have been recognized in Boston, Detroit, Chicago, and New York City.

Age Distribution.—The age distribution in the 24 cases in this series indicates that leptospiral meningitis is a disease of young persons. The range was 10 to 55 years, but 19 of the 24 were under the age of 30 years. This is in line with European experience.[9] The icteric leptospiral infections, on the other hand, tend to occur in persons of middle age.[10] The ages of 12 patients with Weil's disease seen in Grady Hospital during the two-year period of the present study ranged from 25 to 63, averaging 42.

Sex, Race, and Occupation.—Five of the 24 patients were female. Twenty-one of the patients were white; three were Negroes. Occupations mentioned included truck driver, mechanic, machinist, poultry dresser, waitress, and housewife; the majority of the patients were still in school.

TABLE 1.—*Month of Onset of Illness in Twenty-Four Cases of Leptospiral Meningitis*

Month	Number of Cases
January	..
February	2
March	2
April	1
May	1
June	2
July	2
August	10
September	1
October	1
November	2
December	..

Seasonal Incidence.—The seasonal incidence appears to show a distinct grouping of cases in the late summer (see Table 1). Ten of the 24 cases occurred in August, whereas there were none in December or January. The same seasonal variation has also been observed in Europe.[11] The recognition of leptospiral meningitis is facilitated in late summer because physicians are alerted for poliomyelitis at this time; hence spinal fluid examination is likely to be done.

Clinical Features.—Clinical data were meager in some of the records, and tabulation of signs and symptoms by percentages did not seem advisable. The following description is a synthesis of the fairly complete data on our own seven cases, together with such information as was available on the remainder.

7. Larson, C. L.: Leptospirosis in Rats (R. Norvegicus) In and About Washington, D. C.: Evaluation of Methods Used for Diagnosis, Public Health Rep. **58**:949, 1943.

8. Newman, J. P.: Studies on Canine Leptospirosis, Am. J. Vet. Res. **11**:405, 1950.

9. Walch-Sorgdrager, B.: Les leptospiroses, Bull. Health Organ., League of Nations **8**:152, 1939.

10. Molner, J. G.; Meyer, K. F., and Raskin, H. A.: Leptospiral Infections, J. A. M. A. **136**:814 (March 20) 1948.

11. Gsell, O.: Klinik der Leptospirenkrankungen, Ergebn. inn. Med. u. Kinderh. **1**:367, 1949.

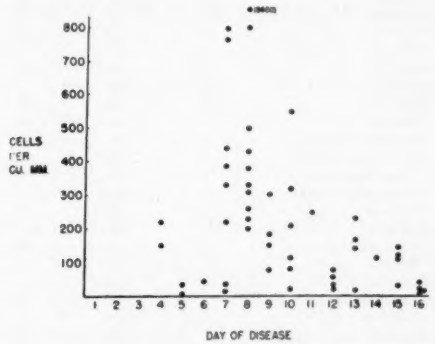
It appears, from inspection of these records, that the severity of symptoms is not sufficient to force early admission to the hospital; most patients remained at home during the first week of illness. The onset of illness was nearly always abrupt, without prodromal manifestations. The principal symptoms were fever, chills, headache, muscle pains, and stiffness of the neck. Apparently all patients had headache, and in most cases it was severe. Pain and stiffness in the neck were mentioned in more than half of the histories; muscle pains in the back and calves were also frequent, but joint pains did not seem common. Photophobia was mentioned only occasionally. Approximately half of the patients had cough. In one of our seven patients cough and hemoptysis were prominent manifestations at the time of admission; in fact, the initial impression was acute bacterial pneumonia. This patient had profuse bloody sputum. Hemoptysis was mentioned in the records of two of the other patients. There was a paucity of gastrointestinal symptoms. One patient had epistaxis.

All patients had fever. The highest temperature recorded was 105.5 F., but the majority had elevations higher than 102 F. at some time. There was no rise in the blood pressure, and pulse rates were proportional to the temperature elevations. This contrasts with descriptions by European writers, which frequently mention bradycardia.[11] Herpes simplex was observed in only one of our seven patients and was not described in any of the cases from outside. This differs from the experience of Troisier and Boquien, who considered it a characteristic finding in leptospiral meningitis.[12] Conjunctival suffusion was noted in four of our seven patients. Two of these, in fact, had areas of conjunctival hemorrhage. It was mentioned in only two of the case reports from the serologic group. Stiffness of the neck was present in all our own patients and was mentioned in the majority of reports on the serologic group. There were no other neurologic signs. Muscle tenderness in the calves and deltoid regions was found in one of our patients and in two of the others in this series. It is almost always present in patients with Weil's disease. Two of the patients had rashes. One of our patients had an eruption on the trunk, consisting of sharply outlined erythematous papules, averaging 5 mm. in diameter. These blanched on pressure. The rash observed in one of the serologic cases was described as "macular, but more extensive than typhoid." Both of these eruptions were observed during only one day. Enlargement of the liver and spleen was not observed, and none of the patients in this group had jaundice.

Routine laboratory tests on blood and urine gave essentially normal findings. The leucocyte count was always within the normal range, although there was sometimes a slight increase in the percentage of polymorphonuclear cells. The urine was normal in all cases. Serologic false-positive reactions on tests for syphilis were not found. Lumbar puncture revealed the spinal fluid pressure to be normal or only slightly increased. In two cases the fluid was normal during the first week of illness, but later showed pleocytosis and increased protein content. In all others there was pleocytosis at the time of the first examination. The highest counts were observed between the 8th and 15th days of illness (Figure). It should be noted that the total cell count seldom exceeded 300, a point of some importance in differentiating this disease from the meningitis of mumps and from lymphocytic choriomeningitis, in which the cell count is likely to be higher than 300. Differential cell counts varied

12. Troisier, J., and Boquien, Y.: La spirochétose méningée, Paris, Masson & Cie, 1933.

somewhat, with the level of polymorphonuclear cells as high as 50% early in the disease. After the 12th day of illness, seldom were more than 30% of the cells polymorphonuclear leucocytes. Spinal fluid protein was usually slightly elevated, but in only two of the cases was it above 100 mg. per 100 cc. The dextrose content was always in the normal range, and in the few instances in which chlorides were determined that value was also normal. The spinal fluid Wassermann reaction was negative. A chest roentgenogram was done in all our cases and in six others in this series, with positive findings in two. In one of our cases the diagnosis at time of admission was acute bacterial pneumonia. The chest roentgenogram on admission, the fifth day of disease, was described as follows: Ill-defined, slightly nodular small densities were seen disseminated throughout both lung fields. Their appearance was not characteristic. No fluid was seen in either pleural space. The process appeared acute and was compatible with a variety of conditions, including virus pneumonia, fungous infection, and disseminated bronchopneumonia. The examiner did not believe that this represented tuberculosis. Reexamination two days later



Spinal fluid cell counts during leptospiral meningitis.

showed the numerous nodular densities previously described, with somewhat more confluence. On the 10th day of the disease there was a remarkable clearing of the previously described generalized pulmonary infiltrations; no free pleural fluid was evident. In one patient from the serologic group a lesion in the right lower lung field was described as a "segmental pneumonitis"; this was said to have cleared completely within five days.

Serologic Tests.—The results of special agglutination tests for leptospirae are shown in Table 2. It will be observed that titers ranged from 1:400 to 1:12,800. Ten of these were against Lept. icterohemorrhagiae, 12 against Lept. canicola, and 2 against Lept. pomona. In some instances positive reactions were obtained with more than one antigen, but in every case there was a clear difference in favor of one of the aforementioned. Antibodies could be demonstrated about the 8th to 10th day of disease, peak titers being attained at the end of the second or third week. In three of six follow-up examinations that have been obtained after 6 to 12 months, the titer was still higher than 1:300, but in all it was lower than during the early convalescent period.

Course of Illness.—Gsell [11] has stressed a biphasic illness with a premonitory grippe-like illness lasting two to three days, followed by a few days with minimal symptoms, then a relapse with meningeal symptoms. The records of our patients do not usually depict this clear differentiation into two phases. Total duration of fever varied from five days to three weeks, the majority of febrile periods lasting 8 to 12 days. Disability following subsidence of fever was not observed, most patients being able to return to regular activity within four to six weeks. Relapse, a common occurrence in Weil's disease, was not recorded in any of these cases.

Sequelae.—No sequelae were observed in any patient in this series. European writers have mentioned the late occurrence of iridocyclitis, from three weeks to one year after the onset of illness. We have observed one patient with probable lepto-

TABLE 2.—*Serologic Test Results in Twenty-Four Cases of Leptospiral Meningitis*

Case	Leptospiral Antigen	Day of Disease	Titer	Day of Disease	Titer
1	Icterohemorrhagiae	9	400	25	12,800
2	Canicola	9	200	15	3,200
3	Canicola	10	< 200	18	1,600
4	Canicola	10	800	17	3,200
5	Canicola	8	< 200	11	400
6	Canicola	10	< 200	16	800
7	Canicola	10	800	175	200
8	Canicola	9	400	15	3,200
9	Pomona	8	< 200	15	400
10	Icterohemorrhagiae	12	400	71	400
11	Icterohemorrhagiae	9	400	15	3,200
12	Icterohemorrhagiae	9	200	25	1,600
13	Icterohemorrhagiae	12	400	19	1,600
14	Canicola	14	6,400	28	6,400
15	Pomona	20	400	..	.....
16	Icterohemorrhagiae	9	< 200	18	1,600
17	Canicola	10	200	45	800
18	Canicola	10	200	27	400
19	Icterohemorrhagiae	4	< 200	39	1,600
20	Canicola	12	800	26	1,600
21	Canicola	16	400	23	800
22	Icterohemorrhagiae	6	800	(2 yr. later)	200
23	Icterohemorrhagiae	25	400	(6 mo. later)	800
24	Icterohemorrhagiae	6	< 200	13	6,400

spiral iridocyclitis in this hospital who had had an illness suggestive of aseptic meningitis seven months previously.[13]

Therapy.—Many of the patients were treated with antibiotics or sulfonamides. It is not possible to state whether any of these had a beneficial effect. In view of the beneficial effect of therapy with penicillin, aureomycin, chloramphenicol (chloromycetin®), and terramycin in experimental leptospirosis, it might be expected that one of these agents would be valuable clinically. However, the variable clinical course and the self-limited nature of the disease make it difficult to assess the results of therapy.

COMMENT

Our findings leave little doubt that leptospiral infection taking the form of benign aseptic meningitis occurs in many parts of the United States. The disease

13. Beeson, P. B.; Hankey, D. D., and Cooper, C. F., Jr.: Leptospiral Iridocyclitis: Evidence of Human Infection with Leptospira Pomona in the United States, J. A. M. A. **145**:229 (Jan. 27) 1951.

has been recognized in other parts of the world for many years. Factors which have tended to prevent more widespread recognition of this disease are the following: 1. The causative organism is not demonstrable by conventional bacteriologic cultural methods. 2. The clinical picture closely resembles that which is evoked by neurotropic virus infection, i. e., lymphocytic cellular exudate in the spinal fluid and normal dextrose content of the spinal fluid. Another difficulty has been that the only satisfactory antigen for serologic diagnosis is living organisms; this has necessitated the maintenance of cultures for the purpose. Preparation of a satisfactory antigen for use in routine clinical laboratories would doubtless lead to increased recognition of all forms of leptospiral infection.

The difference in the blood leucocyte count in the icteric and nonicteric leptospiroses is of interest. When the clinical picture is that of Weil's disease, there is nearly always a leucocytosis (12,000 to 25,000 cells per cubic millimeter). In leptospiral meningitis, on the other hand, the blood leucocyte count is usually between 5,000 and 8,000. We have no hypothesis to explain this striking difference. Leptospiremia and leptospiruria are observed in both forms of illness, so it cannot be said that infection is limited to one organ or tissue in either condition.

SUMMARY

A series of patients with "benign aseptic meningitis" was studied for evidence of leptospiral causation. Positive results were obtained in 6 of a total of 35 patients admitted to one Atlanta hospital during a two-year period. A seventh patient was observed in another Atlanta hospital during the same span of time.

Serologic tests for evidence of leptospiral infection were made on approximately 500 pairs of serums obtained from other localities in the United States. These had been submitted to other laboratories for serologic tests for neurotropic viral infection. It was known, however, that many of them had been collected during epidemics of mumps, poliomyelitis, and encephalitis. Leptospiral agglutinins in titers of probable significance were found in 17 instances.

Data on the seven cases personally observed and on the 17 cases found in the serologic survey permit the following statements:

1. Leptospiral meningitis occurs in many parts of the United States.

2. The clinical features resemble those of meningitides of viral origin, such as mumps, lymphocytic choriomeningitis, and nonparalytic poliomyelitis.

3. Ten of the 24 cases occurred in the month of August.

4. The disease is commoner in males below the age of 30.

Laboratory procedures for the diagnosis of leptospiral infection are described.

EFFECT OF THERAPY ON BLOOD VOLUME, BLOOD PRESSURE, AND SPLEEN SIZE IN POLYCYTHEMIA VERA

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IT HAS LONG been known that marked increases in total blood volume occur in polycythemia vera and that the increase is due primarily to an increase in the total red cell volume.[1] Relatively little, however, has been written concerning serial determinations of the blood volume, total red cell volume, and plasma volume during therapy of this disease. Brown and Giffin [1a] were the first to report on this phase; they studied five patients treated with phlebotomy and x-rays, doing two or three determinations on each patient. Later Haden [2] studied one patient, and shortly thereafter Gibson and associates [1b] reported on a series of three patients studied in a similar manner. Of the nine patients followed by these three groups, eight showed an over-all fall in total red cell volume, associated with a fall in red blood cell count and hemoglobin concentration. The fall in total red cell volume was accompanied with a rise in the plasma volume in six patients and a decrease in two. In the eight patients showing a response to therapy, the total blood volume fell in seven and rose in one. The rise in total blood volume in the latter patient was due to a greater rise in plasma volume than there was fall in total red cell volume. The one remaining patient, whose therapy was apparently inadequate, showed a progressive rise in all three elements (total red cell volume, plasma volume, and total blood volume). In general, the total blood volume, total red cell volume, and plasma volume were much larger in the cases with determinations by the dye method than in those with measurement in this laboratory by the use of labeled red blood cells.[1c]

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1. (*a*) Brown, G. E., and Giffin, H. Z.: Studies of the Vascular Changes in Cases of Polycythemia Vera, Am. J. M. Sc. **171**:157, 1926. (*b*) Gibson, J. G., Jr.; Harris, A. W., and Swigert, V. W.: Clinical Studies of Blood Volume: VIII. Macrocytic and Hypochromic Anemias Due to Chronic Blood Loss, Hemolysis and Miscellaneous Causes, and Polycythemia Vera, J. Clin. Invest. **18**:621, 1939. (*c*) Berlin, N. I.; Lawrence, J. H., and Gartland, J.: Blood Volume in Polycythemia as Determined by P^{32} Labeled Red Blood Cells, Am. J. Med. **9**:747, 1950.

2. Haden, R. L.: The Red Cell Mass in Polycythemia in Relation to Diagnosis and Treatment. Am. J. M. Sc. **196**:493, 1938.

The reported changes in plasma volumes were much less than those in total red cell volume or total blood volume, regardless of whether the change in plasma represented an increase or decrease.

We have considered it worth while to repeat this general type of study for three reasons: (1) to reevaluate blood volume changes during therapy in a larger group of patients with polycythemia vera, using the more reliable method of P^{32}-labeled red blood cells, (2) to determine whether there is significant correlation between changes in blood volume with blood pressure and spleen size, and (3) to evaluate the reliability of serial red cell counts and hematocrit readings for following the upward and downward trend of total red cell volume and blood volume in polycythemia vera.

In view of the frequent association of hypertension with polycythemia vera and the questionable role of hypervolemia as a causative factor in this hypertension, it was felt that serial observations of blood pressure during marked changes in blood volume would help to clarify this problem.

MATERIAL

Twenty patients with polycythemia vera were studied. The diagnosis was established in each case by careful history taking and physical examination and studies of peripheral blood, blood volume, and blood oxygen saturation, in addition to the usual laboratory procedures. The patients' ages ranged from 42 to 81 years, and the known duration of their disease varied from several months to 13 years. In this group there were 12 men and 8 women. The majority of patients received P^{32}, and several were concomitantly treated with phlebotomy and/or Y^{90}.[3] A total of 44 interval determinations of blood volume were made. Some of the patients had not yet reached optimum total red cell volume or blood volume levels at the time these studies were carried out.

METHODS

Blood volumes were determined by the method of Hevesy and Zerahn,[4] as modified in this laboratory, with the use of P^{32}-labeled red blood cells.[1c]

RESULTS

The data are presented in the table and charts. Since the effect of P^{32} on blood volume is brought about primarily by its inhibition of red cell production,[5] we shall present our data in the following way: The change in total red cell volume will be cited first, the accompanying change in plasma volume cited second, and the resultant change in total blood volume stated last. Three general patterns of change were noted during therapy, all of which are seen in the charts.

1. Fall in total red cell volume, parallel fall in plasma volume, and resultant fall in total blood volume—14 instances.

2. Fall in total red cell volume and reciprocal rise in plasma volume, with resultant (*a*) fall in total blood volume when the decrease in total red cell volume

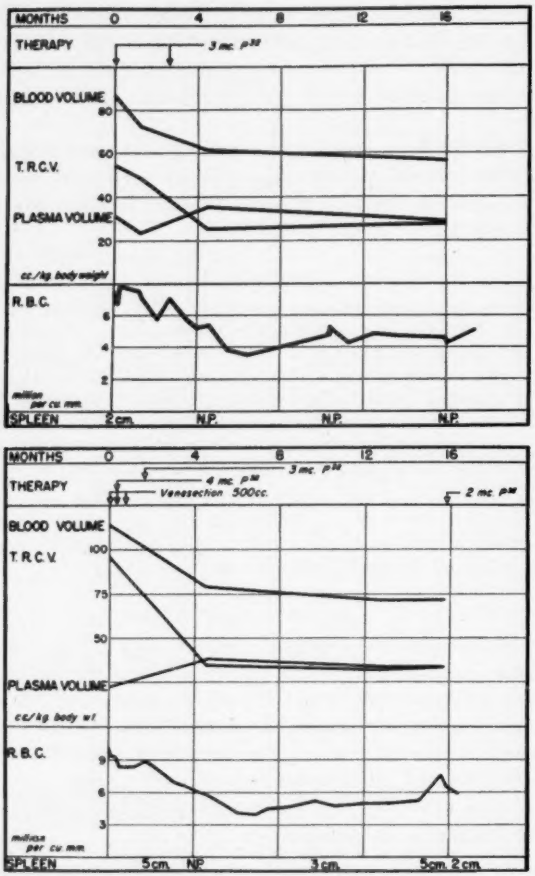
3. Dobson, E. L., and others: Studies with Colloids Containing Radioisotopes of Yttrium, Zirconium, Columbium, and Lanthanum: II. The Controlled Selective Localization of Radioisotopes of Yttrium, Zirconium, and Columbium in the Bone Marrow, Liver, and Spleen, J. Lab. & Clin. Med. **34**:305, 1949.

4. Hevesy, G., and Zerahn, K.: Determination of Red Corpuscle Content, Acta physiol. scandinav. **4**:376, 1942.

5. Lawrence, J. H.: The Control of Polycythemia by Marrow Inhibition: A 10-Year Study on 172 Patients, J. A. M. A. **141**:13 (Sept. 3) 1949.

was greater than the rise in plasma volume—11 instances, and (*b*) rise in total blood volume when the rise in plasma volume was greater than the fall in total red cell volume—3 instances.

3. Rise in total red cell volume—15 instances, with reciprocal fall in plasma volume in 13 and parallel rise in 2. The resultant change in total blood volume again



Results of blood studies and variations in spleen size in two patients (Case 17, top, and Case 8, bottom) receiving therapy for polycythemia vera. *N.P.* indicates not palpable, and *T.R.C.V.*, total red cell volume.

was dependent upon the magnitude of change in total red cell volume and plasma volume. Total blood volume rose in 10 instances and fell in 5.

In one interval there was no significant change in either the total red cell volume or the plasma volume. The magnitude of change in blood volume varied widely in different intervals, as would be expected. The greatest change in total blood volume

was a decrease of 64.9 cc. per kilogram of body weight, occurring during a period of four months, at the beginning of which the patient had received 3 mc. of P^{32} and

Blood Volumes

Case No.	Age	Sex	Date	Blood Volume, Cc./Kg.	Total Red-Cell Volume, Cc./Kg.	Plasma Volume, Cc./Kg.	Hematocrit, Cc./100 Cc.	Red Blood Cells, Millions/ Cu. Mm.
1	70	M	8/31/49	77.6	46.6	30.3	61.0	6.96
			9/12/50	66.4	32.6	33.8	49.0	4.70
2	58	M	4/ 1/49	59.5	24.7	34.8	41.5	4.35
			9/16/49	74.9	40.4	33.7	54.0	5.31
			1/20/50	68.2	34.1	34.1	50.0	6.18
3	79	F	8/ 2/49	85.5	60.2	26.2	70.5	8.86
			3/ 6/50	60.2	37.4	22.8	61.0	6.62
4	81	M	4/29/49	77.4	44.8	32.5	58.0	7.70
			1/28/49	78.6	45.6	33.0	58.0	6.78
			2/17/50	59.8	32.9	26.9	55.0	5.56
5	51	F	3/29/50	103.9	60.2	43.7	58.0	6.45
			7/31/50	88.2	52.9	35.3	60.0	6.00
			1/19/51	73.1	39.8	33.3	54.5	7.30
6	63	M	4/11/50	76.9	51.6	25.3	67.0	8.15
			7/12/50	63.8	35.1	28.7	55.0	6.74
7	46	M	1/21/49	72.7	51.0	21.7	70.0	8.40
			7/ 7/49	65.9	34.3	31.6	52.0	4.80
8	54	M	11/ 2/49	117.4	93.9	22.3	80.0	10.27
			3/14/50	80.0	38.4	41.6	48.0	5.84
			11/27/50	69.0	33.1	35.9	48.0	5.06
			2/19/51	69.9	34.9	35.0	50.0	7.48
9	60	M	4/21/49	75.8	36.5	39.4	48.0	4.95
			6/29/49	70.0	38.5	31.5	55.0	6.00
			8/31/49	82.5	54.4	27.2	66.0	6.90
			10/19/49	84.5	49.9	34.6	59.0	6.44
			5/18/50	92.9	61.1	31.5	66.0	7.67
			8/ 9/50	73.3	42.5	30.8	58.0	7.08
10	..	F	10/11/50	112.9	65.5	47.4	58.0	7.06
			2/ 6/51	48.0	18.7	29.3	39.0	4.98
11	71	M	9/23/49	77.3	42.5	34.0	55.0	5.83
			2/ 1/50	62.6	26.3	36.3	42.0	5.94
			2/28/51	72.0	43.2	29.8	60.0	6.50
12	60	F	6/28/49	57.1	21.7	35.4	38.0	4.60
			1/24/50	58.4	27.7	29.7	47.5	7.31
			3/28/50	67.5	40.5	25.0	60.0	8.06
			8/22/50	64.1	36.5	26.9	57 (58)	5.79
			2/27/51	64.5	36.0	29.4	55.0	6.26
13	60	M	10/11/50	124.5	101.5	23.0	81.5	9.00
			3/30/51	92.0	55.2	25.8	72.0	8.64
14	47	M	3/10/49	63.2	34.0	29.2	54.0	6.25
			8/ 9/49	48.8	23.9	24.9	49.0	4.50
			2/21/50	73.0	44.6	28.4	61.0	6.22
			5/16/50	52.2	28.2	24.0	54.0	5.82
15	42	F	3/15/49	87.2	50.0	37.2	57.0	7.50
			10/12/49	69.0	42.8	25.5	62.0	6.70
			1/ 9/50	72.3	34.7	36.9	48.0	5.74
			11/30/50	70.7	41.0	29.7	58.0	6.12
16	62	M	8/ 3/49	76.2	48.0	27.4	63.0	8.32
			12/ 7/49	70.1	29.4	40.7	42.0	4.90
17	70	M	9/20/49	86.3	54.4	31.1	63.0	7.00
			10/27/49	72.1	48.3	23.1	67.0	7.60
			1/16/50	57.6	27.8	28.9	49.0	4.15
			2/ 2/50	61.3	25.1	35.5	41.0	5.21
18	56	F	4/ 5/49	73.4	41.1	32.3	56.0	6.88
			6/ 3/49	74.1	37.7	36.4	51.0	7.20
			11/30/49	49.9	14.9	35.0	30.0	3.50
			3/ 7/50	46.5	19.0	27.2	41.5	4.22
			2/20/50	53.8	22.6	31.2	42.0	4.72
19	66	F	8/ 2/49	106.8	72.6	33.1	68.0	6.48
			3/13/50	100.6	55.3	45.3	55.0	5.94
			10/18/50	86.8	56.5	30.3	65.0	7.15
20	64	F	2/15/49	80.0	57.6	22.4	72.0	7.26
			4/ 7/49	97.8	49.2	38.6	56.0	5.77
			6/21/50	42.2	15.6	26.1	37.0	4.40

during which time the patient received no additional therapy. The least change was a rise of 0.9 cc. per kilogram of body weight occurring over a three-month period, during which time the patient received no therapy. This is not a significant change. The average change in total blood volume for each interval, including both

rises and falls, was 13.7 cc. per kilogram of body weight, and the average interval between determinations was 4.6 months.

An attempt was made in these 20 patients to determine whether blood pressure was in any way a function of blood volume. Of the 20 patients, 14, or 70%, were hypertensive, a blood-pressure reading of 150/90 or over being the criterion used for classification as hypertensive. This figure is not representative of the percentage of hypertension present in polycythemia vera, since in the whole group of polycythemia vera patients, numbering 154, only 50% were found to be hypertensive.

In four patients the blood pressure data available were inadequate for analysis. In each of the remaining 16, serial blood pressure readings were recorded and compared with serial blood volume values. Five patients, or 31.2%, revealed changes in blood pressure corresponding in direction and time to change in blood volume. Two were hypertensive and three normotensive. Others revealed definite fluctuations in blood pressure, but these were often found to vary oppositely from the blood volume. In view of the relatively wide fluctuations in blood pressure known to occur normally, the significance of these findings is difficult to evaluate. No clear-cut and constant relationship between blood pressure and blood volume could be found. In the total group of 154 polycythemia vera patients, initial blood pressure was plotted versus initial red blood cell counts. No correlation between either systolic or diastolic pressure and red blood cell count was found. These observations are interesting from two standpoints. First, hypertension is common in polycythemia vera (50% in our series of 154 patients). Second, a factor in the maintenance of blood pressure is the blood volume, and one might expect some correlation between an increase in blood volume and an increase in blood pressure. The present investigation lends no support for the view that hypertension in polycythemia vera is dependent upon increased blood volume. The implication here is that even at these red blood cell and blood volume levels the vascular reservoir still possesses enough reserve capacity and distensibility that the blood pressure is not affected.

Spleen size and blood volume relationship was also examined in the same 20 patients. Seven patients revealed a fall in blood volume and a decrease in spleen size over the same time interval. Blood volume determinations were not repeated often enough during this interval to enable us to say whether the rate of decrease was parallel to the rate of decrease in the spleen size. In six patients therapy had been carried on for varying intervals before the first blood volume estimation was done, and the spleen was not palpable at the time of the first volume determination. It was noted that two of these patients subsequently had marked elevations in blood volume, the highest amounting to an increase of 25 cc. per kilogram of body weight. In neither of these patients did the spleen become palpable as the blood volume increased. One other patient had a parallel fall in blood volume and decrease in spleen size over a four-month interval. The spleen decreased from 3 cm. below the costal margin to nonpalpability, while the blood volume decreased from 72 to 62 cc. per kilogram of body weight. However, in a subsequent 16-month period, during which time the blood volume rose to a greater degree than it had fallen (62 to 85 cc. per kilogram of body weight), the spleen did not again increase in size but remained too small to palpate. One patient revealed a reduction in spleen size from 3 cm. below the costal margin to nonpalpability in a one-month interval follow-

ing administration of 3 mc. of Y^{90}. Meanwhile his blood volume was rising from 64 to 74 cc. per kilogram of body weight. Finally, three patients whose spleens were barely palpable at the time of the first blood volume determination showed no change in spleen size, while their volumes dropped 7 to 18 cc. per kilogram of body weight over a 3- to 8-month interval.

In general, it can be stated that with adequate therapy both blood volume and spleen size decrease markedly during therapy of polycythemia vera. It appears, however, from analysis of the blood volume and spleen size changes during therapy that spleen size is definitely not a simple function of blood volume. As pointed out, the spleen not uncommonly remains constant in size while the blood volume changes markedly, or its size may vary oppositely from the blood volume. In many cases the decrease in spleen size appears to be related more closely, in terms of time relationships, to previous irradiation therapy than to blood volume changes. However, we have no direct evidence to support an irradiation effect on the spleen as being responsible for the decrease in size.

Red blood cell counts and hematocrit determinations were done with each of the 44 blood volume determinations. The red blood cell counts and hematocrit readings tended to follow the upward or downward trend of total red cell volume. In eight instances, or 18.0%, the red blood cell count varied oppositely from the total red cell volume. Likewise, in six instances, or 13.5%, the hematocrit varied oppositely from total red cell volume. Similar correlation of red cell count and hematocrit with total blood volume was done. In 15 instances, or 34%, the red cell counts varied oppositely from the total blood volume. The hematocrit was found to vary oppositely in the same percentage of instances, namely, 34%.

Thus, it is seen that serial determinations of red cell counts and hematocrits are only fair criteria for following the upward and downward trends of total red cell volume. They are of even less value for predicting changes in total blood volume. Their unreliability is explained by the marked changes in plasma volume seen in the table. A large increase or fall in plasma volume may produce distinct changes in red cell count and hematocrit, when in reality the total red cell volume is not changing at all.

COMMENT

It can be seen from these data that with adequate therapy in polycythemia vera blood volume falls. This fall in total blood volume assumes two dominant patterns, the frequency of each being approximately equal: (1) a parallel fall in total red cell volume and plasma volume and (2) a fall in total red cell volume with a reciprocal rise in plasma volume. When plasma volume is seen to rise reciprocally, the magnitude of change is usually considerably greater than when it falls. At present we have no understanding of the factors controlling the plasma volume under these conditions or of those which cause the plasma volume to fall in one instance and rise in another while the total red cell volume is decreasing. Nor does the pattern remain constant in individual patients. Patterns 1 and 2 often appear in the same patient at varying intervals of blood volume change. The red blood cell count and the hematocrit vary oppositely from total blood volume in a large percentage of instances. However, in the majority of instances, change in red blood cell count and hematocrit parallels change in total red cell volume. This, however, will not permit an accurate quantitative prediction from the change in red blood count or

hematocrit of the change in total red cell volume. A more satisfactory means of evaluating the response to therapy is serial determination of the blood volume and total red cell volume.

The incidence of hypertension in this small group is inordinately high, being 70%. More reliable figures are represented by the 50% noted in our total series, of which these patients are a part, and the 40% reported by Tinney and associates [6] in their patients. Approximately one-third of the patients sustained a fall in blood pressure concomitant with falling total blood volume. In the other two-thirds the blood pressure remained the same or varied oppositely. No simple or constant relationship between blood volume and blood pressure was demonstrated.

CONCLUSIONS

Serial blood volumes were determined in 20 patients with polycythemia vera. During the fall in blood volume following therapy two patterns were predominant: (1) a fall in total red cell volume and a fall in plasma volume, with resulting fall in total blood volume and (2) a fall in total red cell volume and a rise in plasma volume, with resulting fall in total blood volume. The factors which control plasma volume under these conditions are not known. The frequency of Pattern 1 and of Pattern 2 is about equal. The largest total volumetric change was 64.9 cc. per kilogram of body weight. The average change was 13.7 cc. per kilogram of body weight. The average interval between determinations was 4.6 months.

No simple or constant relationship could be noted between blood volume changes and rise or fall in blood pressure. This was true for both hypertensive and normotensive patients.

The size of the spleen decreased rapidly and to a marked degree after therapy in all but one of the patients in whom the organ was originally palpable, and remained smaller for varying periods. The changes in spleen size did not appear to be a direct or simple function of blood volume.

One cannot accurately judge changes in blood volume in polycythemia vera by red blood cell count or hematocrit. Both varied oppositely from the total blood volume in 34% of instances.

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6. Tinney, W. S.; Hall, B. E., and Giffin, H. Z.: Cardiac Diseases and Hypertension in Polycythemia Vera, Proc. Staff Meet., Mayo Clin. **18**:94, 1943.

L-ARTERENOL (LEVOPHED®) IN THE TREATMENT OF SHOCK DUE TO ACUTE MYOCARDIAL INFARCTION

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THE OCCURRENCE of severe shock following myocardial infarction has generally been considered of such grave prognostic import as almost to negate the possibility of effective therapy. It remains true that shock is a grave prognostic indication, but it is encouraging to find more investigators directing their attention to a reasonable therapeutic approach. Inasmuch as the degree of shock is not necessarily in direct proportion to the size of the infarct, it is not unlikely that the resolution of the shock state could lead to recovery in a proportion of the patients who now succumb.

Rosenbaum and Levine [1] reported a 51% mortality rate for cases of infarction complicated by moderate shock and a 93% mortality for those with severe shock. They considered the prognosis grave if the blood pressure remained at 80 mm. Hg or less for any length of time. Katz and Mintz [2] found that a systolic blood pressure of 90 mm. Hg for several days was a poor prognostic sign and that shock held serious prognostic significance. Billings and co-workers [3] noted a mortality of 79% in case of circulatory failure accompanying myocardial infarction. Unfortunately, few authors have detailed the criteria for their gradations of the severity of shock; hence it is not possible to compare closely the types of cases and recovery rates in the different publications. Nevertheless, there is no disagreement with regard to the mortality rate in cases of myocardial infarction complicated by severe circulatory collapse.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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Boyer [4] has recently reviewed the problem of cardiogenic shock and certain possible methods of treatment. The exact mechanism of this form of shock is still unknown, but that it is different from oligemic shock is now generally accepted. Boyer beneves that neurogenic mechanisms may play a role, but that the bulk of evidence points to inadequate left heart output associated with a redistribution of blood and depletion of the arterial side. This is in essential agreement with the concept of "hypokinetic forward failure." [5]

Though the exact mechanisms of shock complicating myocardial infarction cannot be stated, the shock per se is associated with certain definite histologically demonstrable deleterious effects on the myocardium.[6] The inadequate left ventricular output in cardiogenic shock is associated with a decreased head of pressure in the aorta, and this, in turn, leads to impairment of coronary artery blood flow.[7] The result is ischemia of heart muscle not involved by the initial infarction. It is conceivable that this ischemia may enhance the extension of the initial area of infarction or predispose to fresh infarctions. Thus, it is seen that a marked fall in aortic pressure causes coronary artery insufficiency and increasing myocardial ischemia in what is already a severely damaged heart. The rationale of the therapy to be outlined is, therefore, to raise the arterial blood pressure in cases of severe or profound hypotension with the aim of reestablishing an adequate coronary blood flow. Berman and Akman [8] and Silber and associates,[9] following essentially the same rationale, have recently reported the use of intra-arterial blood or plasma transfusions in cases of myocardial infarction complicated by severe shock. It is noteworthy that intra-arterial transfusion is considered to fill the arterial tree with blood quickly [10] and, thus, to combat the redistribution of blood and depletion of the arterial side which enhance the undesirable cycle of inadequate cardiac output and circulatory collapse.

l-Arterenol (nor-epinephrine), a pressor amine, fulfills certain of the theoretical requirements for combating cardiogenic shock. It has been reported consistently to raise the blood pressure in normotensive and hypertensive persons [11]

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and has been used successfully in cases of oligemic shock in which blood therapy alone was not satisfactory.[12] Goldenberg and colleagues [12] and Wilson and Bassett [13] have successfully used *l*-arterenol to prevent the hypotensive phases during sympathectomy. Studies have shown increases in coronary blood flow in dogs after *l*-arterenol injection.[14] *l*-Arterenol can be given in 5% dextrose in water, and thus sodium administration can be avoided in the presence of congestive heart failure. The institution of an intravenous infusion is a simple routine hospital procedure, and, once the solution is running, a trained nurse can obtain the periodic blood-pressure and pulse-rate data, necessary to safe administration. In none of the cases reported by Goldenberg and associates,[15] Swan,[16] and Wilson and Bassett [13] did there occur any untoward cardiac rhythms. The most frequently observed effect on cardiac rhythm was the production of a mild bradycardia. Thus, *l*-arterenol presented itself as a readily administrable substance producing controllable elevations in arterial blood pressure without any known serious side-effects. However, it remained to be seen whether patients with severe cardiac disease could tolerate *l*-arterenol without complications. Of particular concern was the possibility of precipitating ventricular arrhythmias in the presence of known increased myocardial irritability.

METHODS

l-Arterenol [17] solutions were prepared for intravenous use by adding 1.0 mg. of the base to 1,000 cc. of 0.9% sodium chloride or 5% dextrose in water. The rates of administration were governed by the levels of blood pressure attained. The study being oriented on a clinical basis, it was not considered necessary to calibrate carefully the amounts of *l*-arterenol administered per unit time. Early in the course of the study a conservative approach was adopted, and minimal blood-pressure responses were considered satisfactory. In the later cases an attempt was made to sustain arterial blood pressures at more optimal levels.

No attempt was made to use *l*-arterenol as the sole therapeutic agent. Congestive heart failure, when present, was treated in the accepted manners. All cases were followed by frequent blood-pressure and pulse-rate determinations, the longest allowable interval between checks being one-half hour. When the blood pressure could not be obtained by the auscultatory method, the palpatory method was used to determine the systolic value. Electrocardiograms were obtained at varying intervals after the institution of *l*-arterenol therapy in different cases. In a few of the cases it was not possible to obtain electrocardiograms after *l*-arterenol administration was started, and cardiac rhythm had to be judged solely on a clinical basis.

Seven patients with the clinical diagnosis of acute myocardial infarction were treated. In two cases the presence of recent infarctions was confirmed on postmortem examinations. All the patients demonstrated electrocardiographic evidence of recent myocardial infarction. The essential criteria for institution of *l*-arterenol therapy were (1) a clinical diagnosis of recent myocardial infarction and (2) a systolic blood pressure of 80 mm. Hg or less for at least four hours. The latter criterion limited the patients to those with an extremely grave prognosis, this being desirable in view of the unknown effect of *l*-arterenol upon an irritable myocardium.

12. Goldenberg, M.; Apgar, V.; Deterling, R., and Pines, K. L.: Nor-Epinephrine (Arterenol, Sympathin N) as a Pressor Drug, J. A. M. A. **140**:776 (July 16) 1949.

13. Wilson, C. M., and Bassett, R. C.: Maintenance of Vasopressor Tone with Nor-Epinephrine in Extensive Sympathectomy, Univ. Michigan M. Bull. **16**:57, 1950.

14. Goldenberg and others.[12] Tolkow, B.; Frost, J., and Uvnas, B.: Action of Acetylcholine, Adrenalin, and Nor-Adrenalin on Coronary Blood Flow of Dog, Acta physiol. scandinav. **17**:201, 1949. Rodbard, S.: Personal communication to the authors.

15. Goldenberg and others.[11] Goldenberg and others.[12]

16. Swan, H. J. C.: Effect of Noradrenalin on the Human Circulation, Lancet **2**:508, 1949.

17. The *l*-arterenol preparation (levophed®) used in this study was generously supplied by Mr. Frank Kozlicka, of Winthrop-Stearns, Inc., New York 13.

RESULTS

The results of treatment are summarized in the Table. It was possible to obtain significant blood-pressure elevations with *l*-arterenol administration in four of seven patients treated. In two patients the blood pressures were elevated, but not out of shock levels, and in one patient no response was obtained. One patient (W. J. F.), with a recent anterior wall infarction and a previous episode of acute pulmonary edema, survived an episode of severe shock with *l*-arterenol therapy. He was discharged from the hospital after 73 days. His general condition was considered somewhat better than that of any of the other patients treated. One patient (E.T.M.) died shortly after the available *l*-arterenol supply was exhausted. He had shown a good response to treatment, with recovery from shock. Another patient (J. P.), with an excellent blood-pressure response, died in shock five hours after *l*-arterenol administration was discontinued. The clinical status of both these patients was considerably improved while *l*-arterenol was being administered, and it is felt that both patients would have had a better chance for survival if vasopressor therapy had been continued for longer periods. One of these patients (E. T. M.) had postmortem evidence of an old healed myocardial infarct, a recent infarct, and rheumatic mitral and aortic valvular disease; the other patient (J. P.) had had angina pectoris for two years prior to admission.

Four of the six patients that died in shock after an acute myocardial infarction had postmortem or electrocardiographic evidence of an old healed myocardial infarction. Two of these patients had a significant blood-pressure response to *l*-arterenol. Two patients treated had suffered from chronic congestive heart failure before admission, one of them also having had a previous myocardial infarct. It is of interest that the latter patient (F.L.) had an excellent pressor response to therapy.

No consistent trend was noted with regard to predictability of pressor response with *l*-arterenol treatment. Perhaps the study of larger numbers of cases will provide such information. At no time during *l*-arterenol therapy was there noted any change in prevailing cardiac rhythm or any undesirable effect on the existent state of congestive heart failure.

SUMMARIES OF CASES

E. T. M., a 68-year-old white man, was admitted to the hospital approximately seven hours after an acute myocardial infarction. He had previously been treated at the Hines Veterans Administration Hospital for rheumatic heart disease with mitral and aortic valve involvement and auricular fibrillation. His blood pressure, taken by his family physician, was reported to be 130/70 six hours before hospitalization. Initial physical examination revealed the patient to be in profound shock and in moderately deep coma. The skin was pale, cold and clammy, and moderately cyanotic. There were moist rales at both lung bases. The blood pressure was unobtainable, and on auscultation the heart tones were barely audible. The heart rate at the cardiac apex was 100 beats per minute; the rhythm was grossly irregular. One observer reported a transient pericardial friction rub. Treatment for congestive heart failure was instituted, and eventually a palpatory blood-pressure reading of 60/? was obtained. *l*-Arterenol administration was started approximately one hour after hospital admission and approximately five hours after the onset of shock as reconstructed from the history. *l*-Arterenol solution given intravenously at the rate of 28 to 40 drops per minute raised the blood pressure to within the range of 90/? to 98/?. The blood pressure was 104/? when the solution was given at 50 drops a minute. The available supply of *l*-arterenol was exhausted after 17 hours of treatment. The blood pressure fell to 70/? shortly thereafter, and the patient died one and one-half hours after treatment was stopped.

Results of Treatment of Shock Following Recent Myocardial Infarction with l-Arterenol Intravenously

Patient	Age	Cardiac Status	Cardiac Rhythm	Degree of Shock	Duration of Shock, Hr.	Arterial Blood Pressure Before *l*-Arterenol	Maximum Blood Pressure with *l*-Arterenol	Comment
E. T. M.	68	Known rheumatic heart disease and chronic asthmatic bronchitis; recent anterior wall infarction	Auricular fibrillation	Profound	About 5	60/?	104/—	Patient was first treated; approach was very cautious; no change in cardiac rhythm occurred during therapy; available supply of *l*-arterenol was exhausted after about 17 hr. of treatment; blood pressure fell to 70/? shortly thereafter; patient died 1½ hr. after *l*-arterenol treatment ended
W. J. F.	59	Recent anterior wall infaret; episode of acute pulmonary edema 2 hr. before *l*-arterenol therapy started	Sinus	Severe	About 6	80/?	120/86	Intravenous *l*-arterenol solution infiltrated twice; both times blood pressure fell significantly; *l*-arterenol was given 5 hr., with no change in cardiac rhythm during that time; patient recovered and was discharged after 73 hospital days
J. P.	65	Recent myocardial infarction; angina pectoris of 2 yr. duration	Auricular flutter with 2:1 conduction	Profound	Over 10	80/?	164/90	*l*-Arterenol solution infiltrated once, with resultant significant fall in blood pressure; *l*-arterenol administration stopped after about 8 hr. of treatment; blood pressure gradually fell thereafter, and 17 hr. after administration was stopped patient died in shock and pulmonary edema
J. T. M.	56	Previously hospitalized with hypertensive heart disease and heart failure; acute myocardial infarct while in hospital; ECG showed stigmata of old and recent anterior wall myocardial infarction	Sinus	Profound	Over 10	0/0	80/?	Patient's status complicated by upper gastrointestinal hemorrhage, with coffee-ground vomitus and tarry stools, subsequent to exhibition of anticoagulant therapy; he died 50 min. after *l*-arterenol treatment was started; no change in cardiac rhythm during therapy
C. C. B.	67	Recent anterior wall myocardial infarction and congestive heart failure	Sinus	Profound	Over 5	0/0	0/0	Patient was essentially in preterminal state when *l*-arterenol therapy was started; he died 15 min. after therapy was started, with no change in cardiac rhythm or clinical status
F. L.	58	Chronic congestive heart failure; left bundle branch block; history of myocardial infarct 2 yr. before admission; recent myocardial infarct	Sinus	Profound	5½	0/0	130/? 110/96	Infiltration of *l*-arterenol solution was inadvertently discontinued by nurse after 8½ hr. of treatment; no change in cardiac rhythm while solution was running; blood pressure fell to 0/0 shortly after *l*-arterenol therapy was stopped; when *l*-arterenol was restarted, pressure rose to 90/?, but patient died 45 min. thereafter
D. T.	58	Diabetes mellitus; ECG showed recent posterior wall infarct superimposed on old anterior wall infaret	Sinus	Profound	4	0/0	90/?	Was subjectively improved during *l*-arterenol treatment, with no change in cardiac rhythm; sudden thrashing about and death after 4 hr. of intravenous administration of *l*-arterenol

The admission electrocardiogram on this patient had revealed auricular fibrillation and a classic pattern of acute anterior wall myocardial infarction. Follow-up electrocardiograms 15 and 16 hours after *l*-arterenol therapy was started showed continued auricular fibrillation.

W. J. F., a 59-year-old white man, was transferred to the Hines Veterans Administration Hospital from another hospital eight days after an acute myocardial infarction. On admission the blood pressure was 120/70. The pulse rate was 80, and the cardiac rhythm was regular. An electrocardiogram showed regular sinus rhythm and a recent anterior wall myocardial infarct. On the 11th hospital day the patient suddenly displayed dyspnea and profuse perspiration. The blood pressure at this time was 0/0, the pulse rate 220, and the rhythm regular. An emergency electrocardiogram was obtained one-half hour after the onset of this event, at which time the pulse rate had already returned to 90. The electrocardiogram showed a regular sinus rhythm. Nevertheless, the dyspnea became worse, and the patient coughed up blood-tinged sputum. Treatment with morphine sulfate, tourniquets, digitoxin, and oxygen resulted in relief from the pulmonary edema, but the blood pressure rose only to 80/? and the patient remained in shock. Administration of *l*-arterenol solution was started six hours after the onset of shock. The blood pressure rose to 100/85 when *l*-arterenol was given at 20 drops a minute and to 118/74-84 when the rate of administration was 36 to 42 drops per minute. On two occasions the solution infiltrated, and the intravenous flow had to be restarted; both times there was a significant fall in blood pressure, but at neither time did the pressure fall below 90/70 prior to the resumption of therapy. *l*-Arterenol was given for a total of five hours, during which time a regular sinus rhythm persisted. There was definite clinical improvement. For the next eight days the patient's blood pressure varied between 90/70 and 100/80. Two days after *l*-arterenol therapy the patient exhibited a grossly irregular cardiac rhythm. An electrocardiogram showed auricular fibrillation. The patient had no further episodes of shock and was discharged after 73 hospital days, with a regular sinus rhythm and a blood pressure of 110/70.

J. P., a 65-year-old white man, was admitted to the hospital with a history of sudden onset of breathlessness. He had suffered from recurrent precordial pain, precipitated by effort, with radiation down the left arm, for two years. On admission he was acutely ill, with dyspnea, orthopnea, bilateral moist lung rales, and slight cyanosis. Funduscopy revealed moderate arteriovenous nicking. The blood pressure was 138/96 and the apical pulse rate 176. Cardiac rhythm was regular. An electrocardiogram revealed auricular flutter with 2:1 conduction and was compatible with a recent myocardial infarction. Treatment for pulmonary edema was given and digitalization started. On the following morning the patient's condition was poor. His blood pressure was 100/80, and the apical pulse rate was 160. An electrocardiogram showed persistence of the auricular flutter. Shortly thereafter the patient became cold and clammy and passed into a semicomatose state. The blood pressure fell to 80/?. *l*-Arterenol administration was started 10 hours after the patient began to go into shock and at a rate of 48 to 54 drops a minute increased the blood pressure to 124/90. There was manifest clinical improvement. The blood pressure fell to 94/64 when the intravenous infusion infiltrated. After flow of the solution was restarted, an administration rate of 48 drops a minute raised the blood pressure to 164/90. *l*-Arterenol therapy was stopped after eight hours of treatment, after which the blood pressure fell slowly over the course of six hours to 120/80. The patient died in shock and pulmonary edema approximately 17 hours after pressor therapy was discontinued.

Electrocardiograms 5 and 6.5 hours after the institution of *l*-arterenol treatment showed persistent 2:1 auricular flutter.

J. T. M., a 56-year-old white man, was admitted to the hospital for the treatment of hypertensive arteriosclerotic heart disease and chronic congestive heart failure. He had previously been digitalized. On admission he manifested dyspnea, orthopnea, and moderate ankle edema. There were bilateral moist pulmonary rales. The blood pressure was 170/110, and the cardiac rate was 90 at a regular rhythm. An electrocardiogram showed left heart strain, with a deep Q wave in Lead V_4. The patient's condition improved after treatment for heart failure, and he was ambulatory, when, on the 16th hospital day, after an enema, he suddenly showed marked weakness, dyspnea, and profuse perspiration. The blood pressure was 180/120. The pulse rate increased to 110. An emergency electrocardiogram showed changes compatible with an acute myocardial infarction. Serial records confirmed the diagnosis of a recent anterior wall infarct

superimposed on an old healed anterior wall infarction. Therapy was started with heparin and bishydroxycoumarin (dicumarol®) shortly after the acute episode. Sixteen hours after the institution of anticoagulant treatment, the patient vomited coffee-ground material and had a tarry bowel movement. The blood pressure at this time was 70/?; the pulse rate was 120 with a regular rhythm. The heart tones became almost inaudible. Treatment with whole blood and methamphetamine (methedrine®) hydrochloride raised the blood pressure to 90/?, but the patient remained in shock. The blood pressure then fell to 0/0. An electrocardiogram at this time revealed a regular sinus rhythm at a rate of 130. Intravenous administration of *l*-arterenol solution was started, and at a rate of 60 drops a minute the blood pressure rose to 80/?. Nevertheless, the shock persisted, and the patient died 50 minutes after the exhibition of *l*-arterenol and about 12 hours after going into shock.

H. C. C. B., a 67-year-old Negro man, had dyspnea with the production of blood-tinged sputum approximately four hours before hospital admission. He suffered no pain with the dyspnea. On admission he was noted to be severely dyspneic and orthopneic. Moist rales were heard in both lung fields. The blood pressure was 120/?, and the pulse rate was 130 with a regular rhythm. Treatment for pulmonary edema was instituted. One and one-half hours after admission the blood pressure was 60/?. At this time the patient was semicomatose and in severe shock. An electrocardiogram revealed sinus tachycardia and the classic pattern of an acute anterior wall myocardial infarction. Treatment with saline solution and plasma intravenously, caffeine and sodium benzoate, and epinephrine raised the blood pressure to 130/90. There was an improvement in the patient's general condition. However, five and one-half hours later he again went into severe shock, the pulse rate and blood pressure being unobtainable. Treatment with *l*-arterenol solution was started five and one-half hours after the onset of the second episode of shock, the patient being in a preterminal condition at that time. Fifteen minutes thereafter he died, having had no blood-pressure response to *l*-arterenol solution administered at the rate of 60 drops per minute.

H. F. L., a 58-year-old white man, had suffered from recurrent pulmonary edema for two years prior to admission. This difficulty was initiated subsequent to a myocardial infarction. The patient was admitted to the hospital at this time because of sudden severe dyspnea and belching, the same symptoms which had preceded his first myocardial infarction. Examination revealed him to be markedly dyspneic and orthopneic. Funduscopy disclosed moderate arteriovenous nicking. There were moist rales in both lungs. The left heart border was percussed at the left anterior axillary line in the fifth interspace. A systolic gallop was heard at the cardiac apex; the heart rate was 106, and the rhythm was regular. Blood-pressure readings taken within an hour of admission were 110/? and 98/72. There was slight cyanosis of the fingernail beds. An electrocardiogram revealed a sinus tachycardia and left bundle branch block and was compatible with a recent atypical myocardial infarction. Treatment with mercurials, oxygen, aminophylline, and morphine sulfate resulted in improvement. The patient had been fully digitalized prior to admission. On the second hospital day he suddenly exhibited severe dyspnea, epigastric pain, and marked weakness. The blood pressure at this time was 90/?. His condition again improved with treatment, and the blood pressure rose to 112/80. On the third hospital day his heart rate varied between 106 and 112 beats a minute. In the early morning of the fourth day in the hospital the patient became confused, began fighting to get out of the oxygen tent, and manifested marked dyspnea. He broke into a profuse perspiration; his skin became cold and clammy, and he became comatose. The blood pressure was unobtainable. The heart rate was approximately 130, as determined by auscultation at the cardiac apex, and the rhythm was regular. Administration of *l*-arterenol solution was started five hours after the onset of profound shock. The blood pressure was readily raised and was maintained between 100/70 and 110/96 when the solution was infused at 36 to 44 drops per minute. Nevertheless, there was no striking improvement in the patient's general condition. Electrocardiograms taken 1, 5, and 7.5 hours after intravenous use of *l*-arterenol was started all showed regular sinus tachycardia. Eight and one-half hours after pressor therapy was started, the nurse inadvertently discontinued the intravenous infusion. The blood pressure quickly fell to 0/0. The infusion of *l*-arterenol solution was restarted, but at 60 drops a minute the blood pressure returned only to 90/?. The patient died 45 minutes after infusion of *l*-arterenol was resumed.

D. T., a 58-year-old white man, a known diabetic for two years, suffered excruciating precordial pain, with radiation down the left arm, three and a half hours before hospital admission.

He was given morphine sulfate by his family physician prior to admission. On arrival at the hospital the patient's blood pressure was 110/85. The pulse rate was 120 and the rhythm regular. The chest was clear. His skin was pale, cool, and clammy. An electrocardiogram revealed a recent posterior wall myocardial infarction superimposed on an old anterior wall infarction. Sinus tachycardia was present. Twenty-two hours later the patient went into profound shock. The blood pressure was unobtainable. The apical heart rate was approximately 100, at a regular rhythm. One unit of plasma given intravenously was of no value, and the patient lapsed into coma. Intravenous *l*-arterenol therapy was started four hours after the onset of profound shock. The blood pressure rose to 90/? when the rate of administration was 40 drops a minute. The patient responded to questioning. He had no dyspnea but was restless. Four hours after *l*-arterenol administration was started he displayed sudden marked dyspnea and restlessness. Death occurred shortly thereafter.

COMMENT

l-Arterenol solution was intravenously administered to seven patients with recent myocardial infarction complicated by severe or profound shock. In no instance was any untoward effect noted on the prevailing cardiac rhythm, the state of congestive heart failure, or the subjective status of the patient. Two patients manifesting auricular fibrillation and auricular flutter, respectively, showed no change in rhythm with *l*-arterenol therapy.

It would appear that *l*-arterenol is a favorable vasopressor drug for use in cases of recent myocardial infarction complicated by shock. This drug was found to be readily and safely used under the proper precautions. The choice of cases herein reported was such as to represent an extreme test for any possible medicament. The ability to achieve a satisfactory blood-pressure response in four of the seven patients was surprising, inasmuch as all the patients were direly ill. In view of the absence of deleterious effects, it would appear advisable to start *l*-arterenol therapy earlier than was done during this study. Moreover, our results also suggest that the therapy should be maintained until the patient's general status has shown definite improvement, and that the intravenous infusion should be slowed gradually rather than stopped abruptly.

Obviously, vasopressor therapy can be expected to be of significant value for only a relatively small proportion of the patients who now die in severe or profound shock following myocardial infarction. We do feel that this grave event, cardiogenic shock, should be treated and that the most efficacious treatment now available is with vasopressor drugs. Perhaps further studies will show that intra-arterial transfusion, followed by intravenous use of *l*-arterenol, will achieve relief from cardiogenic shock when *l*-arterenol or intra-arterial transfusion alone is ineffective. These two methods might complement each other in that intra-arterial transfusion fills the arterial tree and *l*-arterenol induces, enhances, and/or maintains the peripheral vasoconstriction necessary to sustain an adequate blood pressure.

SUMMARY

Seven patients with acute myocardial infarction complicated by severe or profound shock were treated with *l*-arterenol intravenously. Significant arterial blood-pressure elevations were attained in four of the seven patients. In no instance was any untoward effect noted on the prevailing cardiac rhythm, the state of congestive heart failure, or the subjective status of the patient.

While the administration of *l*-arterenol in this small series of patients did not give evidence of any untoward effects, its use should still be approached with caution. Further observations are indicated with respect to both its advantages and its disadvantages. Likewise, from this limited experience, no conclusion can be drawn in regard to the bearing this treatment had on ultimate mortality. The results are sufficiently encouraging to justify further careful clinical evaluation of the use of *l*-arterenol in cardiogenic shock following recent myocardial infarction.

104 S. Michigan Ave. (Dr. Miller).

WHIPPLE'S DISEASE

Review of the Literature and Report of Two Cases

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WHIPPLE, in 1907, described a "disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues." [1] The case he reported was "characterized by gradual loss of weight and strength, stools consisting chiefly of neutral fat and fatty acids, indefinite abdominal signs, and a peculiar multiple arthritis." In naming this syndrome he decided upon "intestinal lipodystrophy," which term has been used since; however, this name has recently been shown not to be fully appropriate.

The disease is encountered predominantly in middle-aged men. The usual duration of symptoms has been one to five years. Abdominal symptoms have been indefinite, although some patients presented sharp or colicky abdominal pains. Progressive loss of weight, weakness, lassitude, and, later, a progressive diarrhea were prominent symptoms. Migratory arthritis, generally with an absence of fever, was another frequent complaint. Hypotension, with brown pigmentation of the skin and oral mucosa, often suggested the possibility of Addison's disease.

The disease is characterized anatomically by two principal lesions. The mesenteric lymph nodes are involved by a pronounced lipogranulomatosis, and the tunica propria of the small intestine becomes laden with large, foamy macrophages and may, or may not, contain dilated lymph channels.

Table 1 represents a complete list of all the reported cases of Whipple's disease.[2] All the cases from both the foreign and the domestic literature are included. The two cases to be reported here are included in this table.

From the Department of Pathology, University of Wisconsin Medical School, and the Department of Surgery of the State of Wisconsin General Hospital.

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2. (*c*) Whipple.[1] (*b*) Fahr, T.: Zur Frage des Zusammenhanges zwischen Stoffwechselstörungen und morphologischen Veränderungen im Reticuloendothelialen System, Klin. Wchnschr. **7**:1787-1791 (Sept. 16) 1928. (*c*) Fleischmann, R.: Ueber tumorbildende Fettgewebsgranulome im Gekörse des Dünndarms, Arch. klin. Chir. **158**:692-701, 1930. (*d*) Jarcho, S.: Steatorrhoea with Unusual Intestinal Lesions, Bull. Johns Hopkins Hosp. **59**:275-289 (Oct.) 1936. (*e*) Hill, J. M.: Mesenteric Chyladenectasis: Report of Case, Am. J. Path. **13**:267-276 (March) 1937. (*f*) Korsch, H. J.: Fettstoffwechselstörung mit Granulombildung in Mesenterium, Zentralbl. allg. Path. u. path. Anat. **71**:337-344 (Dec. 30) 1938. (*g*) Glynn, L. E., and Rosenheim, M. L.: Mesenteric Chyladenectasis with Steatorrhoea and Features of Addison's Disease, J. Path. & Bact. **47**:285-290 (Sept.) 1938. (*h*) Gaertner, K.: Über einen Fall von hochgradiger Fettspeicherung in den Mesenteriallymphknoten, Frankfurt. Ztschr. Path. **52**:529-537, 1938.

In past reviews several authors have tried to determine which cases are acceptable and which are not. Because the cause of the syndrome still remains obscure, a certain degree of confusion has resulted from the fact that each author's criteria differed; therefore, certain cases have been considered as examples of Whipple's

(*i*) Hansen, K., and von Staa, H.: Die einheimische Sprue und ihre Folgekrankheiten (sekundäre Avitaminosen), Leipzig, G. Thieme, 1936, p. 39; cited by Clemmesen, J.: Steatorrhoea Arthro-Pericarditica (Mesenteric Chlyadenectasis): Review and Report of Case, Acta med. scandinav. **121**:495-524, 1945. (*j*) Jeckeln, E.: Zur Pathologie der einheimischen Sprue, Arch. path. Anat. **303**:393-405, 1939. (*k*) Reinhart, H. L., and Wilson, S. J.: Malabsorption of Fat (Intestinal Lipodystrophy of Whipple): Report of a Case, Am. J. Path. **15**:483-492 (July) 1939. (*l*) Kloos, K.: Ueber eine eigenartige Fettresorptionsstörung und ihre Beziehung zur Sprue, Arch. path. Anat. **304**:625-658, 1939. (*m*) Sailer, S., and McGann, R. J.: Lipophagic Granulomatosis of Enteric Tract, Am. J. Digest. Dis. **9**:55-63 (Feb.) 1942. (*n*) Apperly, F. L., and Copley, E. L.: Whipple's Disease (Lipophagia Granulomatosis), Gastroenterology **1**:461-470 (May) 1943. (*o*) Vaux, D. M.: Chyladenectasis with Steatorrhoea, J. Path. & Bact. **55**:93-96 (Jan.) 1943. (*p*) Escudero, P.; Mosto, D., and Landabure, P. B.: Lipodistrofia intestinal de Whipple, Arch. Soc. argent. anat. **7**:139-163, 1945. (*q*) Amsterdam, H. J., and Grayzel, D. M.: Intestinal Lipodystrophy (Lipophagia Granulomatosis or Whipple's Disease), Am. J. M. Sc. **210**:605-611 (Nov.) 1945. (*r*) Fitzgerald, P. J., and Kinney, T. D.: Intestinal Lipodystrophy (Whipple's Disease), Am. J. Path. **21**:1069-1089 (Nov.) 1945. (*s*) Clemmesen, J.: Steatorrhoea Arthro-Pericarditica (Mesenteric Chyladenectasis): Review and Report of Case, Acta med. scandinav. **121**:495-524, 1945. (*t*) Oliver-Pascual, E.; Galan, J.; Oliver-Pascual, A., and Castillo, E.: Un caso de lipodistrofia intestinal con lesiones ganglionares mesentérica de granulomatosis lipofágia (enfermedad de Whipple), Rev. españ. enferm. ap. digest. **6**:213-226 (May-June) 1947. (*u*) Rosen, M. S., and Rosen, S. H.: Intestinal Lipodystrophy of Whipple: Report of Case and Analysis of Literature, Am. J. Path. **23**:443-461 (May) 1947. (*v*) Frei, R.: Über die histopathologischen Veränderungen am Dünndarm bei Störungen der Fettresorption (sog. Xanthomatose des Dünndarms), Schweiz. Ztschr. Path. u. Bakt. **10**:685-702, 1947. (*w*) Newman, B., and Pope, R. H.: A Case of Intestinal Lipodystrophy (Whipple's Disease) Simulating Boeck's Sarcoid, Gastroenterology **11**:120-126 (July) 1948. (*x*) Chapnick, H. A.: Idiopathic Steatorrhea, with Report of a Case of Whipple's Disease, Ann. Int. Med. **29**:549-558 (Sept.) 1948. (*y*) Rutishauser, E.; Demole, M., and Mach, R. S.: Sprue Due to Intestinal Lipostasis (Intestinal Lipodystrophy; Whipple's Disease), Rev. méd. Suisse Rom. **68**:573-580 (Sept.) 1948. (*z*) Jones, F. A., and Paulley, J. W.: Intestinal Lipodystrophy (Whipple's Disease), Lancet **1**:214-216 (Feb. 5) 1949. (*a'*) Schultz, P. J.; Benner, W. H., and Christian, W. A.: Intestinal Lipodystrophy (Whipple's Disease), Am. J. Med. **7**:553-563 (Oct.) 1949. (*b'*) Copland, S. M.; Colvin, S. H.; Essrig, I. M., and Heibner, W. C.: Intestinal Lipodystrophy or Whipple's Disease, Surgery **26**:688-698 (Oct.) 1949. (*c'*) Kampmeier, R. H., and Peterson, J. C.: Whipple's Disease: Its Relationship to the Rheumatic State, Tr. Am. Clin. & Climatol. A. **61**:248-268 (Oct.) 1949. (*d'*) Hendrix, J. P.; Black-Schaffer, B.; Withers, R. W., and Handler, P.: Whipple's Intestinal Lipodystrophy: Report of 4 Cases and Discussion of Possible Pathogenic Factors, Arch. Int. Med. **85**:91-131 (Jan.) 1950. (*e'*) Plummer, K.; Russi, S.; Harris, W. H., Jr., and Caravati, C. M.: Lipophagic Intestinal Granulomatosis (Whipple's Disease): Clinical and Pathologic Study of 34 Cases, with Special Reference to Clinical Diagnosis and Pathogenesis, Arch. Int. Med. **86**:280-310 (Aug.) 1950. (*f'*) Reveno, W. S.: Intestinal Lipodystrophy (Whipple's Disease): Report of a Case, New England J. Med. **243**:216-220 (Aug. 10) 1950. (*g'*) Blumgart, H. L.: Three Fatal Adult Cases of Malabsorption of Fat, Arch. Int. Med. **32**:113-128 (July) 1923. (*h'*) Collins, A. N., and Berdez, G. L.: Chyle Cysts of Mesentery, Arch. Surg. **28**:335-344 (Feb.) 1934. (*i'*) Boeck, in discussion on Bargen, J. A.: Bollman, J. L., and Kepler, E. J.: Diarrhea of Pancreatic Insufficiency, Am. J. Digest. Dis. **4**:728-732 (Jan.) 1938. (*j'*) Pearse, H. E.: Whipple's Disease, or Intestinal Lipodystrophy, Surgery **11**:906-911 (June) 1942. (*k'*) Pemberton, J. de J.; Comfort, N. W.; Fair, E., and Zaslow, J.: Intestinal Lipodystrophy (Whipple's Disease): Preliminary Report of 3 Cases in Early Stage of Disease, Surg., Gynec. & Obst. **85**:85-91 (July) 1947.

disease by some and have been either discarded or overlooked by others. Although I do not plan to discuss this problem, it should be noted that there are nine previously reported cases which were considered unacceptable by all the authors because of either incomplete histopathological data or anatomic findings at variance with

TABLE 1.—*Reported Cases of Whipple's Disease*

Author	No. of Cases	Year	Sex	Age	Duration Symptoms, Yr.	
					Arthritic	Abdominal
Whipple [1]	1	1907	M	36	5½	½
Fahr [2b]	1	1928	M	44	6	..*
Fleischmann [2c]	1	1930	M	38	..	½
Jarcho [2d]	1	1936	M	37	15	2
Hill [2e]	1	1937	M	60	..	1
Korsch [2f]	1	1938	M	60	10	1
Glynn and Rosenheim [2g]	1	1938	M	44	..	1
Gaertner [2h]	1	1938	M	32	4	1
Hansen and von Staa [2i]; Jeckeln [2j]	1	1939	M	55	6	4
Reinhart and Wilson [2k]	1	1939	M	74	..	1
Kloos [2l]	1	1939	M	41	5	5
Sailer and McGann [2m]	1	1942	M	45	5	½
Apperly and Copley [2n]	1	1943	M	51	4	4
Vaux [2o]	1	1943	M	49	..	9
Escudero and others [2p]	1	1944	M	27	1	1
Amsterdam and Grayzel [2q]	1	1945	M	54	0	2
Fitzgerald and Kinney [2r]	1	1945	M	48	..	1
Clemmesen [2s]	1	1945	M	27	12	..
Oliver-Pascual and others [2t]	1	1947	F	34	0	16
Rosen and Rosen [2u]	1	1947	F	54	..	½
Frei [2v]	1	1947	M	43	5	..
Newman and Pope [2w]	1	1948	M	50	0	2
Chapnick [2x]	1	1948	M	37	0	1½
Rutishauser [2y]	1	1948	?	?	?	?
Jones and Paulley [2z]	1	1949	M	44	..	1
Schultz and others [2a']	1	1949	M	35	2½	1
Copland and others [2b']	1	1949	M	62	15	11
Kampmeier and Peterson [2c']	4	1949	M-3 F-1	11-47 13	.. to 12	¼-6
Hendrix and others [2d']	4	1950	M	33-56	1½-6	½-3
Plummer and others [2e']	1	1950	M	50	0	1
Reveno [2f']	1	1950	M	56	6	..
Russo	2	1951	M	45-64	0-5	..-2
Blumgart [2g']	3	1923	M-2 F-1	32-44	..	1½ to 2
Collins and Berdez [2h'] (Case 2)	1	1930	F	48	..	½
Boeck [2i']	1	1937	M	45	..	1
Pearse [2j']	1	1942	M	59	13	15
Pemberton and others [2k']	3	1947	M-1 F-2	58-65	.. to 17	1/6-3
Total	48					

* Not specified.

those described by Whipple. These were cases presented by Blumgart,[2g'] Collins and Berdez,[2h'] Boeck,[2i'] Pearse,[2j'] and Pemberton and associates,[2k'] and they are listed as the last nine cases in Table 1. These cases were not included in the data in Table 2; consequently, the latter table is based upon the data accrued from the 39 acceptable cases to date.

The incidence of Whipple's disease may be higher than is apparent, for there may be many cases which have been diagnosed as Hodgkin's disease, leukemia,

Addison's disease, Boeck's sarcoid, ulcerative colitis, sprue and other nutritional deficiency diseases, idiopathic steatorrhea, various mesenteric lymphadenopathies, bacillary or amebic dysentery, and carcinoma of the head of the pancreas or in the gastrointestinal tract. Since the diagnosis of this disease can be made only by histological examination of the mesenteric lymph nodes and/or the small bowel, either exploratory laparotomy, with biopsy of the mesenteric nodes, or autopsy is the only means for diagnosis. The disease has been primarily recognized at necropsy, and to date only eight cases have been accurately or presumptively diagnosed before death.[3]

REPORT OF CASES

CASE 1.[4]—The patient, a 45-year-old white man, was admitted with a chief complaint of weakness and diarrhea. This illness commenced two years prior to admission and was characterized by bouts of diarrhea lasting two or three days. Although a liquid medicine prescribed by his physician seemed to stop the diarrhea, he suffered recurrences every two or three months. Six months before this final admission, the severity and frequency of the diarrhea increased; 8 to 12 watery stools associated with gas pains were passed daily. The diarrhea was worse at night. Because of failure of treatment to alleviate his condition, he attended the McCleary Clinic in Missouri, where some relief was obtained. But the diarrhea recurred, in one instance after an emotional upset. Although his appetite was fairly good, he lost 30 lb. (13.6 kg.) during the course of the illness. A review of systems revealed an essentially normal condition, except for migratory arthritis of five years' duration which affected the back, hips, ankles, and shoulders without residua. Past illnesses included measles, mumps, chickenpox, and scarlet fever. In the family history there were diabetes mellitus (father, mother, and sister), cancer (uncle), and tuberculosis (cousin).

Results of Physical Examination.—The patient was an emaciated man who appeared older than his stated age. The skin was warm and dry. Several palpable cervical lymph nodes were observed. The lungs were clear on percussion and auscultation, and the heart, of normal size by percussion, was normal on auscultation. Blood pressure measured 98 systolic and 86 diastolic. The abdomen was flat, tense, and rigid, with generalized tenderness on deep palpation. By rectal examination no masses were observed, although the anal sphincter was spastic. Results of both funduscopic and neurologic examinations were normal.

Laboratory Data.—The observations available from the McCleary Clinic included a report on a urinalysis showing a 1+ reaction for albumin, occasional hyaline and granular casts, occasional red blood cells, and 12 to 15 pus cells per high-power field. Gastric analysis disclosed no free acid after histamine administration. The hemoglobin levels were 5.75 and 7.4 gm. per 100 cc., with corresponding red blood cell counts of 3,300,000 and 3,900,000 per cubic millimeter. Both the white blood cell count and the differential count were normal. In three instances the stools contained blood; they were acid on two occasions and on two other occasions contained increased quantities of fat, said to be characteristic of idiopathic steatorrhea. No ova or parasites were found in the stools. On sigmoidoscopic examination the suggestion of "chronic ulcerative colitis" was raised; the process was believed to be in the quiescent stage of Crohn and Rosenberg.

Further laboratory studies were completed at the Wisconsin General Hospital. The urine was acid, with a specific gravity of 1.001. The hemoglobin concentration was 6.7 gm.; red blood cells were 3,690,000 and leucocytes 7,200 per cubic millimeter. The hematocrit reading was 27.25%. The measured values for the red cells were as follows: volume index, 0.8; cell volume, 73.74 cu. μ; saturation index, 0.73, and sedimentation rate, 8 mm. per hour. Blood sugar was 93 mg. and nonprotein nitrogen 50 mg. per 100 cc. Serologic tests for syphilis, typhoid, paratyphoid, Brucella, and tularemia organisms gave negative reactions. The stools were positive for blood by the gum guaiacum test, contained no amebae, ova, or parasites, and were grossly normal. A roentgenogram of the chest showed no significant pulmonary or cardiac disease. With the use

3. Footnote 2 *t*, *x*, *c'* to *f'*.

4. This case was reported previously by Altshuler, C. H., in Clinicopathologic Conferences, Wisconsin M. J. **50**:185-188 (Feb.) 1951.

of a barium sulfate enema questionable masses were visualized, both in the rectosigmoid and at the splenic flexure. In the gastrointestinal series the esophagus, stomach, and duodenum were normal, and there was hypomotility of the small bowel. Proctoscopic examination was unsatisfactory because of thick, dried fecal material. A tuberculin reaction was negative.

Course.—The patient became weaker rapidly and was stuporous by the seventh day. The blood pressure fell to 74 systolic and 50 diastolic. He failed to respond to three blood transfusions of 500 cc. each, with additional fluids given parenterally, and died on the 10th hospital day.

Necroscopy Observations.—At autopsy (45:149) the significant pathological alterations were limited to the abdomen. In the mesentery there were numerous large, discrete lymph nodes. On section these had a characteristic honeycombed, sponge-like appearance. The spaces contained fatty material. The bowel was grossly normal.

On microscopic examination, the lamina propria of the small intestine was thickened by an infiltration of large mononuclear cells, with a granular eosinophilic cytoplasm. The cells simulated those seen in Gaucher's disease. Like the latter, they gave a positive reaction with the periodic-acid-leuco-fuchsin technique. In addition, a few large vacuoles were seen in the mucosal epithelium. The mesenteric lymph nodes were permeated by numerous large clear vacuoles, many of which were lined by irregular foreign-body type giant cells. In parts of the nodes there were fibrosis and a nonspecific granulomatous reaction.

The second case remained a clinical diagnostic problem, and, in spite of extensive laboratory studies, was undiagnosed until the time of autopsy, when the diagnosis became obvious.

CASE 2.—*First Admission.*—This man, aged 64, was first admitted to the hospital April 1, 1950, with a history of progressive severe weakness of one year's duration and a weight loss of 46 lb. (20.9 kg.) in the previous three years. There was no history of hemoptysis, hematemesis, hematuria, bloody or tarry stools, nausea, vomiting, or abdominal pain. Generally his appetite had decreased, but he was still eating one good meal daily. His bowel habits were regular, twice daily. In the past year there were four episodes of unconsciousness, associated with twitches and shakes, but no incontinence or tongue biting. There was no history of headaches, vertigo, tinnitus, or diplopia.

He had a chronic cough for the past two or three years, productive of about one-half cup (about 120 cc.) of greenish sputum per day. There was some palpitation associated with dyspnea. He had had a dry, scaly erythematous eruption of his legs for the past year. No history of arthritis was elicited. The past medical history was negative except that he had been told that he had tuberculosis which was not active. His father had died of tuberculosis in 1904. The patient had been born in Hungary and had come to the United States in 1910. Daily alcohol intake was strictly in moderation.

Results of Physical Examination: The temperature was 98 F., the pulse rate, 74, the respiration rate, 26, and the blood pressure, 90/55. The patient was thin, emaciated, weak, and sallow. The skin was dry and scaly. There were red, dull, scaling lesions on both legs. A soft generalized adenopathy was present; the nodes were discrete and movable. The funduscopic examination revealed arteriosclerotic changes. The heart and lungs were normal, except for a soft apical systolic murmur. The abdomen was flat; no tenderness or mass was present; the liver edge was palpable just below the costal margin. Results of rectal examination were normal. Slight pitting edema of the feet was present. Neurologic examination showed an essentially normal condition.

Laboratory Studies: The results of urinalysis were not remarkable. The initial hemoglobin value was 12.3 gm., and the red blood cells were 3,900,000; on discharge hemoglobin concentration was 10.2 gm., and red blood cells numbered 3,500,000. White blood cells numbered about 10,900, and the differential count showed 80% neutrophiles, 15% lymphocytes, 3% monocytes, and 2% eosinophiles. The sedimentation rate was 56 mm.; the hematocrit reading was 39%. The blood sugar was 107 mg.; nonprotein nitrogen, 33 mg.; serum calcium, 10.8 and 9.8 gm., and phosphorus, 2.8 and 3.6 gm. per 100 cc. The Wassermann reaction was negative. Blood sodium was 135 mEq. and potassium 4.2 mEq. per liter. Smears and cultures of the sputum were negative for acid-fast organisms. Serum protein was 6.5 gm., with an albumin-globulin ratio of 3.1/3.4, and on another occasion, 3.3/3.2. Alkaline phosphatase was 9 units. Routine typhoid and paratyphoid agglutinations were negative (except for a 1:40 titer to the "H" antigen in the typhoid agglutina-

tion). On studies of the sputum for fungi, the only one found by culture was Candida albicans. A Kepler water test and an eosinophilic count to rule out adrenal insufficiency both had normal results. Bone marrow findings were not remarkable, except for increased cellularity. Smears and cultures of the bone marrow were negative for Histoplasma. Chest roentgenograms showed inflammatory disease in the central and lower part of the right lung, and a calcified tuberculous nodule was present at the left apex. On the right side the differentiation between tuberculous and nontuberculous inflammatory disease could not be made. Skull-sinus films were normal. Bronchograms on the right were normal except for unsatisfactory filling in the right upper lobe; on the left, minimal to moderate bronchiectasis was seen. Roentgen visualization after a barium sulfate enema revealed a normal colon and terminal ileum. An upper gastrointestinal series was essentially normal except for some coarseness in the descending duodenum, which was felt to be insignificant. Roentgenograms of both hands were normal except for nonspecific decalcification. Biopsy specimens of the axillary nodes on two occasions showed a granulomatous lesion, with sarcoid, tuberculosis, brucellosis, and histoplasmosis as the principal diagnostic considerations. Dermatological opinion was that the skin lesions probably represented psoriasis. Fluoroscopy of the chest revealed a normal condition. Reactions to first- and second-strength tuberculin and coccidioidin skin tests were negative. A skin test reaction was positive to histoplasmin, but a blood culture was negative. Studies for Brucella gave negative results.

Hospital Course: The patient continued to have marked weakness, asthenia, emaciation, and hypotension in spite of supportive therapy. During the latter part of the hospital stay his course was complicated by diarrhea, consisting of five to seven stools per day. The patient was generally afebrile except for an occasional slight temperature elevation.

Second Admission.—During the eight months after discharge the patient was up and about, but with progressive weakness and emaciation. Two weeks before admission he became weaker and bedridden, increasingly irritable, and confused at night. He also was troubled with diarrheal stools but had no complaints of pain. He was able to take about 1 pt. (473 cc.) of fluid daily and small amounts of soft diet.

Results of Physical Examination: A respiratory arrhythmia was present, with a rate of 9 to 14 per minute. The skin was dry and scaly. The peripheral lymph nodes were markedly smaller, as compared with their size on the previous admission, being barely palpable in the cervical and inguinal regions. There were moist crepitant rales at both lung bases. The heart was not enlarged and had a regular rate of 54 per minute and no murmurs. The blood pressure was 64/24. The abdominal examination yielded no positive findings. There was a reddish-brownish discoloration of both legs, with dry scaling of the skin and 3+ edema of the legs, sacrum, and scrotum.

Laboratory Studies: Urinalysis revealed the specific gravity to be 1.014 to 1.017. Albumin ranged from 0.07 to 0.125 gm. per 100 cc. Microscopic study showed 1 to 3 white blood cells and 6 to 8 red blood cells per high-power field. Two to eight casts were present per low-power field. Blood studies disclosed a hemoglobin level of 8.9 to 11.2 gm. per 100 cc. and 2,870,000 to 3,180,000 red cells and 9,200 to 17,700 white cells per cubic millimeter, with a differential count of 73 to 85% filamented cells, 9 to 10% nonfilamented cells, 3% lymphocytes, and 3 to 2% monocytes. Blood sugar was 110 mg., nonprotein nitrogen, 33 to 49 mg., and total protein, 4.6 to 5.3 gm., with an albumin to globulin ratio of 2.0/2.6 to 2.7/2.8, per 100 cc. Tests for vitamin A tolerance elicited a normal response. Serum sodium was 143 mEq., and serum potassium, 3.4 to 4.6 mEq. per liter. Calcium was 11.5 gm. and phosphorus 3.0 mg. per 100 cc. The stool was negative for ova and parasites. The stool guaiac test gave a 2+ reaction. Carbon-dioxide-combining power was 41 vol. %. The spinal fluid was normal. Kepler's test gave abnormal results, but the epinephrine-eosinophile test showed a normal eosinopenic response. Blood cultures were negative. Urine culture showed bacilli of the colon group. One stool analysis was reported as negative for neutral fats and fatty acids. An abdominal roentgenogram showed an abnormal amount of gas. Visualization with a barium sulfate enema was normal except for a few diverticula. An electrocardiogram showed marked nonspecific changes.

Course: Supportive therapy, including blood, fluids, and potassium chloride for the hypopotassemia, was instituted. Biopsy of an axillary mass showed it to be cystic, and microscopic interpretation was an old abscess. Interpretation of a biopsy specimen of a supraclavicular node was consistent with sarcoidosis. Stools were large, soft, yellow, and foamy. The temperature was

afebrile except for three days during mid-hospital course and the three terminal days, when an elevation to 101 F. was recorded. The course was progressively downhill, and death came on the 37th hospital day.

Autopsy Examination (51 : 30).—Gross Observations: Multiple decubitus ulcers were present over the usual bony prominences. There was no palpable general lymphadenopathy or abdominal mass.

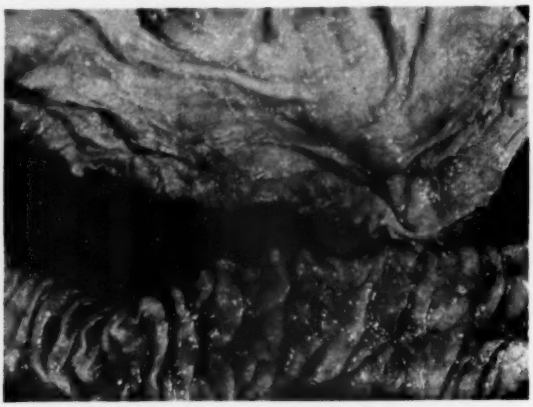

Fig. 1.—Jejunum: Fibrous thickening and gray-white patches on serosa shown above; thickened mucosa shown below.

Fig. 2.—Mesentery, illustrating large, doughy, "honeycombed" lymph nodes exposed by a transverse cut.

There was 200 cc. of a yellow, slightly cloudy fluid in the peritoneal cavity. The peritoneal surface was generally dull and thickened in appearance and was studded with innumerable gray-white areas, the largest of which measured 3 to 4 mm. across. There were fibrous adhesions in the left upper quadrant concentrated about the spleen.

Bilaterally the pleural surfaces were dull, thickened, and covered with patches similar to those in the peritoneum. There was no pleural fluid, but both lungs were covered with many dense fibrous adhesions. There was no hilar or mediastinal lymphadenopathy. The pericardial cavity

Fig. 3.—Characteristic thickening of tunica propria of the jejunum containing large vacuolated spaces (× 75).

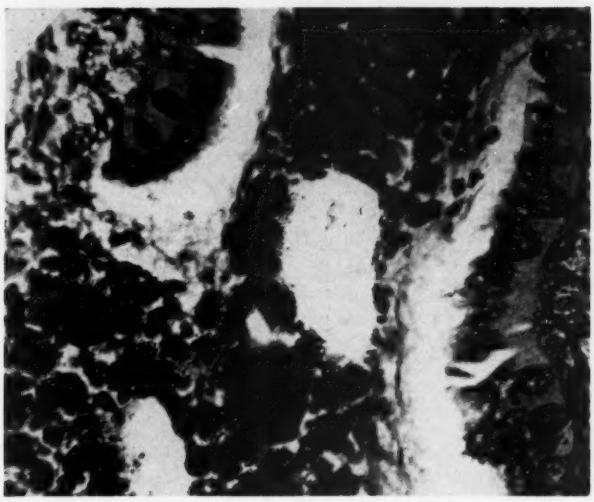

Fig. 4.—Schiff's periodic acid stain of jejunal mucosa to demonstrate foam cells filled with glycoprotein granules (shown as black in photomicrograph); × 350.

revealed marked thickening of the parietal and visceral layers. There were also fibrous and fibrinous adhesions in the pericardial sac, but no excessive fluid was present. There was serous atrophy of the subepicardial fat. The myocardium was softer and browner than usual. Along the line of closure of the leaflets of the aortic valve were located firm, shiny, fibrous-like, non-vegetative verrucae. The other valves were not remarkable. The coronary arteries showed marked atherosclerotic changes, as did the aorta. Both lungs revealed a rather marked pulmonary edema on cut section, as well as scattered patchy areas of bronchopneumonia.

The stomach and duodenum revealed no abnormality. The entire length of the jejunum and ileum had a grayish, greasy appearance to the serosa, and the wall of the small intestine was thickened and doughy in consistency (Fig. 1). The mucosa was grayish and fatty in appearance and was studded with yellowish-white flecks. The large bowel was normal except for scattered diverticula of the sigmoid.

The mesentery had the same general grayish appearance, and all the mesenteric lymph nodes were enlarged to a varying degree, the largest measuring 4 cm. in diameter (Fig. 2). They were soft and doughy, and on section the normal architecture was replaced by a "honeycombed"

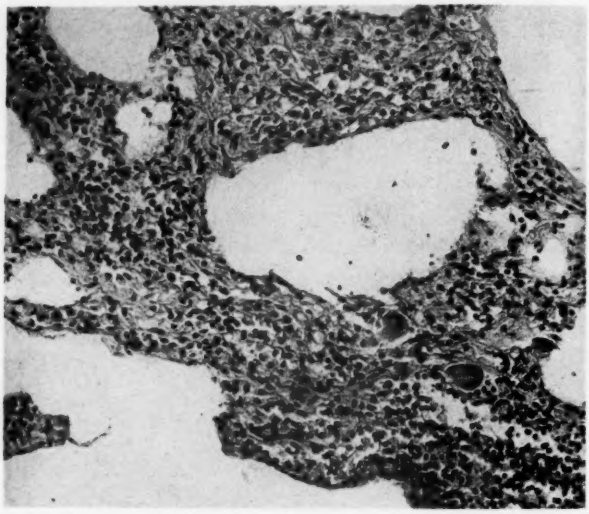

Fig. 5.—Mesenteric lymph node, showing characteristic vacuolated spaces ("Swiss-cheese" appearance), foreign-body giant cells, foam cells, and fibroplasia (× 150).

alteration from which exuded a yellowish-white creamy material. Postmortem smear and culture of this material were negative. The retroperitoneal lymph nodes were similarly involved.

The liver, gall bladder, and pancreas were all grossly normal. The splenic capsule was markedly thickened; the pulp was pale and soft. The adrenal glands showed no gross lesion, and the kidneys were not unusual except for some cysts in the left kidney.

Microscopic Observations: Striking fibrous thickening of the epicardium and serous atrophy of the subepicardial fat were noted. The myocardium showed some increased interstitial fibrous tissue with scattered mononuclear cells. A section through the aortic valve showed swelling and degeneration of the collagen fibers beneath the verrucae.

The lungs revealed severe pulmonary edema throughout all sections. Scattered areas of mild to severe bronchopneumonia were seen.

The spleen was surrounded by a thick hyalinized fibrous capsule. Increased cellularity, predominantly mononuclear, was present in the red pulp, and an occasional multinucleated giant cell was seen.

The liver, gall bladder, pancreas, stomach, and colon were not abnormal.

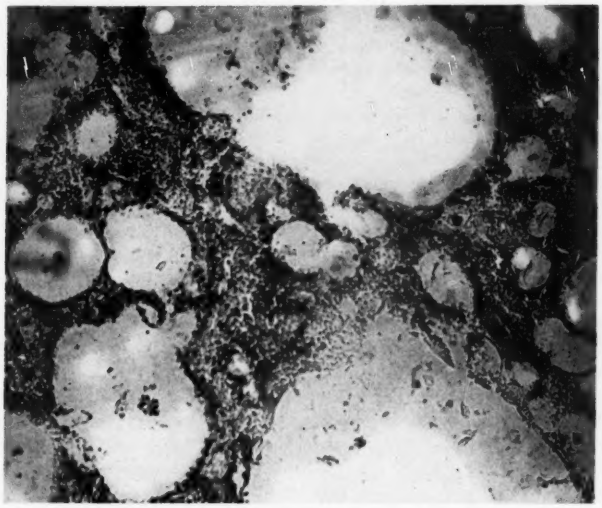

Fig. 6.—Mesenteric lymph node stained with Sudan IV. Vacuolated spaces were intensely sudanophilic (appear as grayish areas in this illustration); × 75.

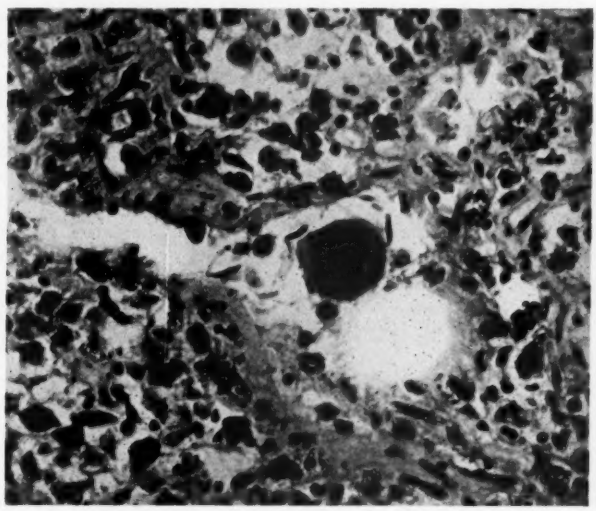

Fig. 7.—Mesenteric lymph node stained with Schiff's periodic acid stain to show glycoprotein, as dark granules, in both macrophages and giant cells (× 350).

Sections of the jejunum and ileum revealed that the tunica propria was markedly thickened, due to the presence of innumerable large mononuclear foam macrophages. These cells had an eosinophilic granularity in the cytoplasm when stained with hematoxylin and eosin (Fig. 3). There were also large vacuolated spaces in the tunica propria that represented dilated lacteals. Sections stained for fat did not show any sudanophilic material in the foam cells or vacuolated spaces; however, sections with Schiff's periodic acid stain showed that the granules in the foam cells stained a brilliant scarlet (Fig. 4).

Examination of the mesenteric lymph nodes revealed loss of recognizable architecture, and there was complete replacement by a lipogranulomatous process. This was manifested by the appearance of small and large vacuolated spaces, giving a "Swiss-cheese" picture to the nodes. These spaces were surrounded by large foam cells and multinucleated foreign-body giant cells (Fig. 5). There was a diffuse fibroplasia throughout the nodes, and no lymph follicles were seen. Fat stains of the nodes revealed the vacuolated spaces to be intensely sudanophilic, as were many of the surrounding macrophages (Fig. 6). Sections with the periodic acid stain demonstrated that many of the macrophages and giant cells stained an intense scarlet (Fig. 7). In the supporting stroma were scattered lymphocytes, plasma cells, and monocytes. In addition, some areas contained nonspecific granulomatous reactions.

Other sections of the adrenal glands, kidneys, urinary bladder, testes, bone marrow, pituitary, and brain did not show anything unusual.

Diagnoses.—The diagnoses were as follows: Whipple's disease; emaciation; atherosclerosis of aorta and coronary arteries; marantic endocarditis of aortic valve; pericarditis, fibrous, acute and chronic; pleuritis, fibrous, chronic; peritonitis, fibrous, chronic; pulmonary edema, severe, and bronchopneumonia.

COMMENT

These cases present the characteristic picture of Whipple's disease. Both patients were men, in the usual age range, with progressive weakness, weight loss, and diarrhea. The first patient had a migratory polyarthritis, whereas no such history was elicited from the second. The history of chronic cough, seen in several other reported cases, was present in the second case. The physical findings of emaciation, hypotension, edema, and vague indefinite abdominal signs occurred in both cases, and the usual laboratory findings of anemia, hypoproteinemia, hypocalcemia, and normal adrenocortical function, and negative results on bacterial studies, were present. Gastrointestinal roentgenographic studies showed the usual hypomobility, puddling of the barium sulfate suspension, and thickening of the valvulae conniventes.

The stool analyses in both of these cases were primarily only for blood, ova, and parasites. They did not include extensive studies for fat except for one instance in the second case, and those findings were certainly questionable. In his original case, Whipple [1] found 80% of the dry stool to be fat; 50% was neutral fat, and 30%, fatty acids. In his analysis of the lymph nodes, the ratio of neutral fat to fatty acids was 85 to 15. The majority of authors who have since performed similar studies found results that were in close approximation to those of Whipple, although in a few of the reported cases the findings were within normal range.

The characteristic pathological changes were clearly demonstrated in the small intestine and mesenteric lymph nodes in both cases. Special stain techniques confirmed the observations of Whipple [1] and Black-Schaffer.[5] Sections of the small intestine and mesenteric lymph nodes were stained for fat with Sudan IV. (There were no specimens available for fat stain in the first case, and the following observations were noted: There was no sudanophilic staining material in the tunica

5. Black-Schaffer, B.: Tinctoral Demonstration of a Glycoprotein in Whipple's Disease, Proc. Soc. Exper. Biol. & Med. **72**:225-227 (Oct.) 1949.

propria of the small bowel. The foamy macrophages and the vacuolated spaces did not stain positively with Sudan IV. However, the picture was quite different in the lymph nodes, for it was observed that all the vacuolated spaces and many of the macrophages stained vividly with Sudan IV [Fig. 6].) As Black-Schaffer [5] has pointed out,

> The characteristic intestinal lesion is a crowding of the lamina propria by macrophages containing an isotopic refractile substance which Whipple found unstainable with osmic acid. This observation has been repeatedly overlooked in the literature, almost all authors assuming a lipid nature for this curious substance. . . .
>
> The characteristic enlarged, cystic, fat-filled mesenteric lymph nodes (lipogranulomatosis) are so prominent that they have dominated the approach to the problem.

Sections of similar areas in the small intestine and mesenteric lymph nodes from both cases were then stained with Schiff's periodic acid technique. All the large foamy macrophages in the mucosa stained a deep scarlet, identifying the phagocytosed substance as a glycoprotein (Fig. 6). The mesenteric lymph nodes showed that many of the macrophages, as well as the multinucleated giant cells, stained a brilliant scarlet with this technique (Fig. 7).

In the second case the clinical impression and antemortem microscopic interpretation of the axillary and supraclavicular lymph nodes were suggestive of Boeck's sarcoid. It was of interest to find another somewhat similar case reported by Newman and Pope.[2w] In both cases, however, the diagnosis of Boeck's sarcoid could not be maintained upon review of the biopsy specimens in relation to the observations at autopsy. The surgical specimens probably represented an early phase of the disease that simulated Boeck's sarcoid.

Most authors believe that Whipple's disease represents a clinical entity. The present number of cases reported is sufficient for evaluation of the pertinent clinical, laboratory, and pathological characteristics of the syndrome. A careful review of these characteristics should provide adequate criteria to enable the clinician to establish at least a presumptive diagnosis. The data in Table 2 represent the pertinent findings observed in the 39 acceptable cases. The importance of each characteristic of this syndrome is apparent when the incidence of each is noted; in many of the reported cases a certain number of the findings were unspecified or questionable. Excellent reviews have been presented by Plummer and colleagues [2e'] and Hendrix and associates.[2d']

The diagnosis of Whipple's disease requires differentiation from those diseases that present similar clinical pictures. Usually sprue and the sprue-like syndromes are considered first. Whipple's disease may be distinguished from sprue by its lack of glossitis and macrocytic anemia; in addition, it does not respond to liver extract and folic acid therapy as does sprue. Those diseases which present sprue-like symptoms due to lacteal and lymphatic obstruction perhaps offer even greater difficulty in differential diagnosis. Examples of such cases of lymphatic obstruction are those due to tuberculous mesenteric lymphadenopathy (tabes mesenterica), mesenteric and retroperitoneal lymphomas, and obstructive parasitic infections. The nutritional failure and steatorrhea seen in pancreatic insufficiency may be distinguished from Whipple's disease by the qualitative and quantitative examination of the enzymes of aspirated duodenal contents. These are normal in Whipple's disease, and low levels are seen in pancreatic insufficiency. Also, the abdominal

pain in the latter is more characteristic and is described as a "boring through" to the back. Differentiation of Whipple's disease from the adrenal insufficiency of Addison's disease may be made by the laboratory estimations of serum sodium and potassium levels, both of which are normal in Whipple's disease, as are the results of Kepler's test and the epinephrine-eosinophile-response test.[6] It should be remembered that the characteristic pathological picture of the intestine and mesenteric lymph nodes in Whipple's disease always is the most undisputable point in the differentiation of this syndrome from the other diseases.

TABLE 2.—*Tabulated Data on Thirty-Nine Acceptable Cases of Whipple's Disease* *

Findings	Definitely Present	Definitely Absent	Unspecified or Questionable
History			
Asthenia, weight loss	38	0	1
Abdominal discomfort	33	0	6
Diarrhea	32	1	6
Arthritis	26	9	4
Fever	16	20	3
Blood in stools	13	8	18
Chronic cough	11	6	22
Physical Findings			
Hypotension	27	0	12
Generalized lymphadenopathy	19	6	14
Skin pigmentation	17	9	13
Edema	17	7	15
Abdominal mass	8	16	15
Laboratory Findings			
Anemia (secondary type)	34	3	2
Hypoproteinemia	19	3	17
Steatorrhea	15	3	21
Achlorhydria	13	8	18
Low dextrose-tolerance curve	10	7	22
Hypocalcemia	9	3	27
Leucocytosis	7	20	12
Eosinophilia	5	17	17
Pathological Findings			
Intestinal macrophagocytosis	34	0	5
Lipogranuloma, mesenteric lymph nodes	36	0	3
Glycoprotein stain, intestinal macrophagocytes	6	0	33
Fat stain, intestinal macrophagocytes	5	5	29
Chylous ascites	5	27	7
Fibrous pericarditis	20	11	8
Fibrous pleuritis	15	9	15
Fibrous peritonitis	15	8	16
Marantic endocarditis	13	15	11

* Modified from Hendrix and others.[2d']

Pathogenesis.—The theories of pathogenesis that have been developed since this disease was first discovered are many and varied. Table 3 illustrates in outline form most of the proposed theories. The concepts presented in the earlier reports have, for the most part, been considered inadequate by the more recent authors. After reviewing Table 3, it becomes obvious that the causation still remains obscure. As a causative factor, thoracic duct obstruction may be discarded, for in five instances [6] no obstruction could be found when the thoracic duct was dissected out at autopsy. Also, experimental ligation of the thoracic duct has never produced any lesions comparable with Whipple's disease. All the other theories proposing deranged fat

6. Whipple.[1] Footnote 2 *m*, *c'*, *f'*, and *g'*.

metabolism, absorption of toxic agents, endocrinological disturbances, or a rheumatic state as a cause are based only on past clinicopathological observations; until more cases are observed and are diagnosed earlier, and more investigative procedures are performed, the causation of this syndrome will remain unknown. As Black-

TABLE 3.—*Theories of Pathogenesis* *

Author	Theory
	Chemical or Metabolic
Whipple [1]	Obscure disease of fat metabolism; possible absorption of abnormal fat or fat-containing toxic substance
Korsch [2f]	Chemical alteration of absorbed fat; functional alteration of pancreatic lipase → abnormally split interstitial fat → foreign-body inflammation
Fleischmann [2c]	Lipid necrosis
Sailer and McGann [2m]	Local necrosis of fat tissue → lipolytic ferments
Apperly and Copley [2n]	Faulty fat resynthesis with retention of fatty acids in tissue → inflammatory fibrosis
Gaertner [2h]	Physical alteration of absorbed fat
Hansen and von Staa [2i]; Jeckeln [2j]	Peculiar nontropical sprue complicated by sepsis
Kloos [2l]	Peculiar disturbance of fat resorption
Glynn and Rosenheim [2s]	Possible adrenal insufficiency
Pearse [2j']	Abnormal bile metabolism
Reinhart and Wilson [2k]; Escudero and others [2p]	Increased intestinal excretion and reabsorption of fat
Hass, G. M.: Arch. Path. 26:956-965 (Nov.) 1938	Fatty acids with high melting point → inflammatory reaction
Thannhauser, S. J., in Christian, H. A. and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1921, Vol. 4, pt. 2	Localized xanthoma formation in inflammatory tissue
Stryker, W. A.: Arch. Path. 31:670-692 (June) 1941 (experimental)	Prolonged administration of liquid petrolatum induces comparable changes in intestine and lymph nodes of rabbits
Black-Schaffer [5]; Hendrix and others [2d']	Abnormal function of intestinal epithelium (phagotactic substance is glycoprotein) → impaired absorption of fat, glucose, and perhaps protein; systemic illness or intoxication → inflammation of serous membranes
Plummer and others [2e']	Repeated stress from unidentifiable noxious stimuli → acquired systemic disorder → same end-result as in other adaptation diseases (e. g., adrenocortical exhaustion) → selective depletion of certain corticoid fractions → impaired cortical response → disturbed enzyme equilibrium of phospholipid metabolism
Reveno [2f']	Absence of some key substance or influence of a toxic agent and faulty interaction in the mucosal cell allow incompletely prepared fat to pass through and act as a foreign body leading to eventual obstruction of lymph channels and nodes and ultimately lacteals
	Mechanical or Infectious
Hill [2e]	Lymphangitis → fibrotic obstruction → mesenteric cysts (chylangiectasis)
Jarcho [2d]; Newman and Pope [2w]	Obstructive chylangiectasis, ? congenital
Rosen and Rosen [2u]	Partial obstruction (?) of thoracic duct
Chapnick [2z]	Mesenteric lymphatic obstruction, acquired, ? cause
Clemmesen [2a]	Pararheumatic type inflammation → lacteal fibrosis → obstruction
Kampmeier and Peterson [2c']	Nutritional failure in rheumatic subjects; should include intestinal lipodystrophy in the group of rheumatic or collagen diseases

* Modified after Plummer.[2e']

Schaffer [5] and Hendrix and co-workers [2d'] have pointed out, Whipple's disease does not appear to be due merely to a defective fat metabolism. They suggest that the name intestinal lipodystrophy is not fully appropriate and prefer to call the syndrome "Whipple's disease."

Therapy.—Many efforts at therapy have been made, but no effective method of treatment and management has been found. The usual supportive measures of blood and plasma transfusions, special diets, and vitamin therapy are given to remedy the

nutritional failure. A good discussion of the therapeutics of this syndrome was presented by Reveno,[2f] who was able to try several remedies on his patient, in whom the disease was diagnosed one year before death. Reveno used iron, salicylates, hydrochloric acid, vitamins A, D, and K, and various bile salts, but without effect. Pearse [2j] reported improvement in his patient's condition after bile salt therapy, but this apparently is an isolated instance. Reveno [2f] also used insulin in an attempt to form fats from carbohydrates; choline to aid in the absorption of fat, and folic acid and crude and concentrated liver extract because of their beneficial effect in the treatment of sprue. Commercial pancreatic extracts and raw minced hog pancreas were given for seven weeks, but all failed to produce any improvement. He also found that administration of duodenal contents which had been aspirated from a healthy subject was unsuccessful, as was the administration of bile obtained by surgical drainage from another patient and given by tube in 100-cc. quantities twice daily for 10 days. Hendrix and associates [2d] have suggested that polysorbate 80 (tween® 80), folic acid, and vitamin B_{12} should also be tried.

SUMMARY

Two new cases of Whipple's disease are reported.

A review of all previously reported cases is presented. A tabulation of the pertinent findings is presented for facilitation of clinical diagnosis, and the characteristic features of the syndrome, as well as the differential diagnosis, are discussed.

Possible etiological theories and methods of treatment are discussed.

Case Reports

GASTRIC LIPOMA

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THIS COMMUNICATION presents a case of lipoma of the stomach in which the unique roentgenographic appearance of fatty tissue permitted a preoperative diagnosis. This case also demonstrates clearly the pitfalls in diagnosis of benign tumors of this organ.

REPORT OF CASE

First Admission.—W. R. a 28-year-old man, white, single, truck driver, was first admitted to the hospital on Nov. 11, 1949, with a three-week history of dyspnea on exertion, dizziness, weakness, fatigability, frequent headaches, and anorexia. His physician had treated him for anemia for several weeks without improvement.

On admission physical examination revealed two small nontender axillary nodes. His blood count showed 2,700,000 red cells, 6.6 gm. of hemoglobin, and 5,800 white cells, with 76% neutrophiles, 16% lymphocytes, 7% monocytes, and 1% eosinophiles. Blood smears showed persistent poikilocytosis and anisocytosis. Repeat blood counts demonstrated elevated monocytes to an average of 11%. Sternal marrow studies were reported as showing marked normoblastic hyperplasia. Lymph node biopsy and other tests for blood dyscrasias gave normal results. Two stools were negative for blood, ova, and parasites. A chest roentgenogram was normal. Transfusions of whole blood raised the red cell count to 4,500,000 and the hemoglobin concentration to 13.5 gm.

Roentgen examination of his gastrointestinal tract was not requested during this admission. He was discharged on Dec. 8, 1949, with a diagnosis of anemia of undetermined origin, although a consultant in hematology considered the patient to have monocytic leukemia. The patient remained asymptomatic for nine months.

On Oct. 19, 1950, he had a sudden massive gastrointestinal hemorrhage and passed numerous large, tarry stools. He had some nausea and vomited once. There was no hematemesis. He was readmitted to the hospital.

Second Admission.—On physical examination the patient was a well-nourished man who showed extreme pallor. A Grade I systolic murmur was heard to the left of the sternum. Examination of the abdomen revealed no masses or organs to be palpable.

Laboratory Data: Blood studies showed 2,430,000 red cells, 6.0 gm. of hemoglobin, and 9,500 white cells, with 68% neutrophiles, 29% lymphocytes and 3% monocytes. The hematocrit reading was 21%. A blood smear showed moderate anisocytosis and polychromasia. The urine was normal. Gastric analysis showed no free hydrochloric acid in a fasting specimen and 6 units of free hydrochloric acid following histamine administration, with a total acidity of 33 units. All specimens drawn from the stomach were found to have 4+ reactions for blood. One stool gave a 3+ reaction on guaiac test. Subsequent stools gave negative reactions to tests for blood.

During his second hospital stay a gastrointestinal roentgenographic series was done for the first time.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Results of Roentgen Examination: The preliminary survey film showed a large radiolucent shadow in the left upper abdomen which did not conform to normal gas distribution in the abdomen (Fig. 1). After ingestion of barium sulfate suspension, a large filling defect was demonstrated on the greater curvature of the stomach (Fig. 2). The location of this tumor corresponded with the position of the radiolucent shadow noted on the plain film, indicating the lipomatous character of the neoplasm. The outlines of the tumor were smooth, except at the apex of the mass, where an ulceration measuring approximately 1.5 cm. was present. The possibility of liposarcoma could not be excluded.

Fig. 1.—The patient was a 28-year-old man with known chronic anemia which was followed by massive gastrointestinal hemorrhage. Plain film shows a large radiolucent area in the left upper quadrant (arrows) which does not correspond to normal gas distribution in the abdomen and represents a lipomatous tumor.

Gastroscopy showed a large, globular, smooth mass, with an irregular ulceration. The mucosa was slightly injected. A biopsy specimen removed by gastroscope revealed normal mucosa.

Operation: A large tumor was found on the greater curvature of the stomach. Subtotal gastrectomy and gastroenterostomy were performed.

Pathologic Observations: The specimen contained a large intramural tumor which measured 13 cm. in diameter. The mucosa over the mass was movable, except over the apex, where a circular ulceration 3 cm. in diameter was present. On cut section, the tumor was noted to be submucosal and composed of yellow tissue laced with white strands. There was a definite greasy feeling to the tissue.

Microscopic Observations: The mucosa was normal and showed well-formed gastric glands. Replacing the muscularis was a large collection of adipose cells separated by thick collagenous septa containing many fibroblasts. The ulcerated area extended entirely through the mucosa and was based in tumor tissue.

Diagnosis: The diagnosis was fibrolipoma of the stomach with ulceration.

COMMENT

Incidence.—Benign tumors of the stomach constitute approximately 15% [1] of all gastric neoplasms. Rigler and Ericksen [2] surveyed reports of 6,242 con-

Fig. 2.—After ingestion of barium sulfate suspension, large tumor is outlined on greater curvature of stomach which corresponds to the radiolucent shadow noted on plain film. Gastric ulcer crater over lipoma is well demonstrated.

secutive autopsies in which 194 tumors of the stomach and duodenum were observed. In their series, 25% were benign. In a recent review of 20,000 autopsies performed at one hospital over an 11-year period, Thompson and Oyster [1b] found the over-all incidence of benign gastric tumors to be 0.33%.

1. (*a*) Judd, E. S., and Hoerner, M. T.: Benign Tumors of Stomach, Am. J. Surg. **31**:427-430, 1936. (*b*) Thompson, H. L., and Oyster, J. M.: Neoplasms of the Stomach Other Than Carcinoma, Gastroenterology **15**:185-243, 1950.

2. Rigler, L. G., and Ericksen, L. G.: Benign Tumors of the Stomach: Observation on Their Incidence and Malignant Degeneration, Radiology **26**:6-15, 1936.

Lipomatous tumors are rare. Palmer [3] tabulated references to 103 recorded cases of fatty tumors of the stomach. Eliason and Wright [4] found lipomas to comprise 4.8% of 610 benign tumors of the stomach in cases compiled from the literature. Minnes and Geschickter [5] noted the incidence to be 3.4% of their total of 941 collected cases of benign tumors. In a single hospital series of 94 benign gastric tumors Thompson and Oyster [1b] found only one lipoma (1.1%). The actual frequency of the fatty neoplasm is probably closer to this figure than it is to the estimates derived from published reports. In any case, the rarity of the tumor is well established.

Clinical Findings.—Most benign gastric tumors are found in persons who have no overt gastrointestinal symptoms. Their commonest complaints relate to the effects of anemia due to subclinical recurrent gastric hemorrhages.[6] Blood loss is usually slow and intermittent, resulting from a small ulceration of gastric mucosa over the tumor mass.

According to Judd and Hoerner,[1a] one-third of all benign tumors have gastric ulcers overlying the tumors. Massive hemorrhage, as in the case described, is frequently the presenting complaint and is the major cause of fatality. Other symptoms, such as epigastric distress, nausea, and vomiting, are mainly referable to the shape and site of the neoplasm. If the tumor is pedunculated, or located near the pylorus, intermittent intussusception or obstruction may occur.[7] While a majority of these tumors arise in the antrum, they are found in all sections of the stomach.[3] It is of interest that these tumors are rarely, if ever, large enough or firm enough to be palpable. Gastric acidity values are usually normal.

Diagnosis.—The failure to think of the possibility of gastric lesions in a patient who has chronic anemia is the diagnostic pitfall. Any explanation for a finding of anemia which does not completely satisfy the situation should prompt immediate roentgen investigation of the gastrointestinal tract. There are several cogent reasons for urgency in establishment of the diagnosis. The most important factors are hemorrhage and inanition, which may lead to a fatal outcome.[8] In addition, numerous cases of proved malignant degeneration have been recorded by Rigler and Ericksen,[2] Judd and Hoerner,[1a] and Thompson and Oyster.[1b] The last authors report an over-all mortality of 57.3% in patients with benign gastric tumors and attribute this, in some degree, to the presence of the benign growths.

The age of the patient seems of little value in differential diagnosis. Benign gastric tumors are generally discovered in younger age groups than are other types

3. Palmer, E. D.: Benign Intramural Tumors of the Stomach, Medicine **30**:81-182, 1951.

4. Eliason, E. L., and Wright, V. W. M.: Benign Tumors of the Stomach, Surg., Gynec. & Obst. **41**:461-472, 1925.

5. Minnes, J. F., and Geschickter, C. F.: Benign Tumors of the Stomach, Am. J. Cancer **28**:136-149, 1936.

6. Thompson and Oyster.[1b] Rigler and Ericksen.[2] Palmer.[3]

7. Hobbs, W. H., and Cohen, S. E.: Gastroduodenal Invagination Due to Submucosal Lipoma of Stomach, Am. J. Surg. **71**:505-518, 1946.

8. Thompson and Oyster.[1a] Phelan, W. J., and Rowan, D. E.: Lipoma of the Stomach, Am. J. Surg. **79**:469-472, 1950. Rumold, M. J.: Submucous Lipoma of the Stomach, Surgery **10**:242-249, 1941.

of neoplasms. The patient presented is only 28 years of age, although Palmer [3] has stated that the clinical disease of benign fatty gastric tumor is one of middle and old age.

The lipomatous form of gastric tumor is of special interest because it is possible to make a correct histologic diagnosis based on the roentgenographic findings. Preoperative diagnostic accuracy of the tissue origin of benign gastric neoplasms generally is poor. Palmer [3] has noted the infrequency of correct diagnosis of lipomas prior to surgical intervention.

Roentgenologic Observations.—In the abdomen, the decreased density of fat in comparison with normal tissue components results in an area of increased radiability on the roentgenogram which provides the necessary contrast for differentiation. If large fatty tissue masses are present, their shadows may be confused by the unwary with gas pockets located in various hollow viscera, particularly the stomach and colon. Radiolucent areas must be analyzed for evidence of abnormal distributions and size to avoid missing fat-containing tumors, such as lipomas, teratomas, and dermoid cysts.

Lipomas arise intramurally and develop in the submucosa. Because of its submucous growth, some movement of the tumor independent of the mucosal motion may be visible fluoroscopically, as noted by Culver and Dobrak.[9] This finding, if present, would suggest the benign nature of the lesion. Moore [10] has outlined other valuable roentgenographic criteria for determining benignity of gastric tumors. These may be summarized as follows:

1. A circumscribed filling defect is present.

2. The filling defect is usually on the gastric wall, leaving curvatures regular and pliant.

3. Rugae are obliterated over the tumor, but those surrounding a benign tumor are more nearly normal than those in the presence of malignant or inflammatory lesions.

4. The tumors cause little or no disturbance in peristalsis, and retention is uncommon except when the lesion is at or near the pylorus.

5. They do not reveal a niche or incisura or other evidence of spasm.

6. They are rarely sufficiently large to be palpated.

Treatment.—In all cases of benign gastric neoplasm, surgical treatment is mandatory. The type of operation depends on the size and location of the lesion and upon the philosophy of the surgeon. The dangers of malignant transformation have led some authors to advocate subtotal gastrectomy.[11] The consensus, however, is in favor of local surgical excision with an adequate cuff of tissue.[12]

9. Culver, G. J., and Dobrak, A.: Submucosal Gastric Lipoma, Am. J. Roentgenol. **64**:938-939, 1950.

10. Moore, A. B.: A Roentgenologic Study of Benign Tumors of the Stomach, Am. J. Roentgenol. **11**:61-65, 1924.

11. Dudley, G. S.; Miscall, L., and Morse, S. F.: Benign Tumors of the Stomach, Arch. Surg. **45**:702-726 (Nov.) 1942.

12. Judd and Hoerner,[1a] Balfour, D. C., and Henderson, E. F.: Benign Tumors of the Stomach, Ann. Surg. **85**:354-359, 1927.

CONCLUSIONS

A case of gastric lipoma is presented in which the possibilities and pitfalls in diagnosis of benign gastric tumors are illustrated.

The diagnostic aid of relative radiolucency of lipomas in differentiation of gastric tumors is pointed out.

Emphasis is placed on the frequency of anemia as the only sign of benign gastric tumor.

The necessity for roentgenologic gastrointestinal studies in all cases of inadequately explained anemia is reiterated.

The frequency of gastric ulceration and massive hemorrhage in benign gastric tumors is noted.

FOLLICULAR LYMPHOMA WITH TRANSIENT LEUKEMIC PHASE

Brief Review of Literature and Report of a Case

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A BRIEF review of the literature on blood changes in follicular lymphoma disclosed that in the cases reported by Brill, Baehr, and Rosenthal [1] the blood picture was normal. The majority of later cases also appeared to be associated with normal red blood cell count and hemoglobin values. Sometimes slight anemia was observed.[2] According to Gall and associates,[3] anemia (a count of 3,500,000 red blood cells or less) was found in 18% of their 63 follicular lymphoma cases, compared with an incidence of 39% in their cases of other lymphomas. They frequently noted anemia as a terminal manifestation, perhaps due to long-continued irradiation. Meyer [4] reported marked anemia in one of six cases; moderate anemia in two, and no anemia in three cases. Mayer and Thomas [5] found terminal normocytic anemia in all their cases. The anemia was severe in only two cases. One patient, with normal results on bone marrow study, reacted well to liver therapy and transfusions. In the other one the condition was intractable to treatment.

The most frequent change reported in the white blood cell count is leucopenia.[6] Berman and co-workers [7] reported a case of follicular lymphoma with severe neutropenia and thrombocytopenia ("hypersplenism"). Splenectomy brought about improvement in the thrombocyte count, whereas the neutropenia persisted. According to Symmers,[6c] eosinophilia is rare in follicular lymphoma, in contrast with

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1. Brill, N. E.; Baehr, G., and Rosenthal, N.: Generalized Giant Lymph Follicle Hyperplasia of Lymph Nodes and Spleen, J. A. M. A. **84**:668-671 (Feb. 28) 1925.

2. (*a*) Combes, F. C., and Bluefarb, S. M.: Giant Follicular Lymphadenopathy, Arch. Dermat. & Syph. **44**:409-419 (Sept.) 1941. (*b*) Cohen, S. E., and Bergstrom, V. W.: Giant Follicle Lymphadenopathy, New York J. Med. **49**:273-278 (Feb. 1) 1949. (*c*) Baggenstoss, A. H., and Heck, F. J.: Follicular Lymphoblastoma (Giant Lymph Follicle Hyperplasia of Lymph Nodes and Spleen), Am. J. M. Sc. **200**:17-27 (July) 1940.

3. Gall, E. A.; Morrison, H. R., and Scott, A. T.: The Follicular Type of Malignant Lymphoma: A Survey of 63 Cases, Ann. Int. Med. **14**:2073-2090 (May) 1941.

4. Meyer, O. O.: Follicular Lymphoblastoma, Blood **3**:921-933 (Aug.) 1948.

5. Mayer, S., Jr., and Thomas, H. M., Jr.: Follicular Lymphoblastoma and a Related Form of Lymphosarcoma, Bull. Johns Hopkins Hosp. **64**:315-338 (May) 1939.

6. (*a*) Footnote 2. (*b*) Meyer.[4] (*c*) Symmers, D.: Lymphoid Diseases, Arch. Path. **45**:73-131 (Jan.) 1948.

7. Berman, L.; Klein, A. A.; Linn, H. J., and Bates, G. S.: Hypersplenism Associated with Follicular Lymphoblastoma, Blood **5**:286-292 (March) 1950.

Hodgkin's disease in which it is frequent. The skin lesions probably were responsible for the eosinophilia in the cases of Combes and Bluefarb.[2a]

Abnormal cells may appear in the blood. Mayer and Thomas [5] found a few myelocytes terminally in one case; in another, atypical monocytes. In 6% of their 38 follicular lymphoma cases, Gall and Mallory [8] observed abnormal cells. Custer [9] depicted, in his atlas, monocytosis and monocytoid tumor cells in the blood in a case of follicular lymphoma.

Intravital bone marrow examinations were performed in a few instances. Mayer and Thomas [5] reported normal bone marrow in a case of severe anemia which reacted well to treatment. In one of two reported cases, Cooper and Watkins [10] noted slight increase of the lymphocytes of the bone marrow; the blood of this patient was normal. In the other patient who had just completed a course of irradiation therapy, the bone marrow was hyperplastic, with a preponderance of the myeloid line. The peripheral blood in this patient showed leucopenia with relative lymphocytosis and monocytosis. Rohr [11] showed a photomicrograph of a well-defined lymph follicle (*"Mark-lymphom"*) from a questionable case of follicular lymphoma with some features of aleukemic lymphadenosis.

In autopsies, Terplan [12] noticed numerous lymph follicles in the bone marrow. Cohen and Bergstrom [12a] observed a 64-year-old patient with extensive lymph node and spleen involvement. The red blood cell count was 3,200,000; the white cell count was between 6,950 and 3,550. At autopsy, the bone marrow of the vertebrae and ribs showed "numerous isolated islands of lymphoid tissue comparable in size and shape to the follicles in the nodes and sharply demarcated from the rest of the marrow. . . ." Symmers [6c] recorded cases with autopsies in which the bone marrow was intact.

Reported Cases Ending in or Associated with Leukemia.—Baehr and Klemperer [13] observed in two of their cases throughout a period of years the lymph node changes characteristic of giant follicular lymphoma. These patients had normal blood cell counts. However, terminally they showed leucocytosis, with large numbers of lymphoblasts, so that "if these two patients had been observed only in this terminal stage, the clinical picture could not have been easily differentiated from chronic lymphatic leukemia." Symmers [14] published four cases in which lymphatic leukemia followed or accompanied giant follicular lymphadenopathy. Uhlmann,[15]

8. Gall, E. A., and Mallory, T. B.: Malignant Lymphoma: A Clinico-Pathologic Survey of 618 Cases, Am. J. Path. **18**:381-415 (May) 1942.

9. Custer, R. P.: An Atlas of the Blood and Bone Marrow, Philadelphia, W. B. Saunders Company, 1949, p. 97.

10. Cooper, T., and Watkins, C. H.: An Evaluation of Sternal Aspiration as an Aid in Diagnosis of the Malignant Lymphomata, Blood **4**:534-549 (May) 1949.

11. Rohr, K.: Das menschliche Knochenmark, Stuttgart, Georg Thieme, 1949, p. 310.

12. Terplan, K.: Über eine eigenartige granulom-ähnliche Systemerkrankung, Verhandl. deutsch. path. Gesellsch. **24**:65-72, 1929.

12a. Cohen, S. E., and Bergstrom, V. W.: Giant Follicular Lymphoblastoma, Am. J. Clin. Path. **16**:22-39 (Jan.) 1946.

13. Baehr, G., and Klemperer, P.: Giant Follicle Lymphoma, New York J. Med. **40**:7-11 (Jan. 1) 1940.

14. Symmers, D.: Giant Follicular Lymphadenopathy With or Without Splenomegaly, Arch. Path. **26**:603-647 (Sept.) 1938.

15. Uhlmann, E. M.: The Significance of Giant Follicular Lymphadenopathy, Radiology **50**:147-156 (Feb.) 1948.

among the 22 cases of follicular lymphoma reviewed, found 3 in which the postmortem diagnosis was leukemia. Two of these patients were leucopenic during life, and in one of these the differential count was not indicative of leukemia. In the third patient, during the last months of life the white cell count rose greatly, with a high percentage of lymphocytes. Saxén [16] observed a case that clinically appeared to be lymphatic leukemia. Histologically, the lymph nodes showed the characteristic features of giant follicular lymphoma. This author, however, considers the possibility that his case represents an early stage of lymphatic leukemia. In a discussion on the comprehensive paper of Cohen and Bergstrom,[2b] Dr. Joseph C. Ehrlich mentioned that in the experience gathered at the Lebanon Hospital and Mount Sinai Hospital, New York, "two cases developed a lymphoid leukemic blood picture." Custer and Bernhard [17] described the case of a 20-year-old white man. The photomicrographs demonstrate the simultaneous presence of different histological patterns—follicular lymphoblastoma, syncytial type of reticulum-cell sarcoma, and chronic lymphatic leukemia. The blood picture was that of chronic lymphatic leukemia. Gall and associates [3] mentioned a case of follicular lymphoma with the peripheral blood picture of lymphocytic leukemia. Gall and Mallory [8] observed 38 cases of follicular lymphoma. One case had a leukemic blood picture. In all these cases apparently the leukemic blood picture developed as a persistent feature or a terminal event.

The following is a report of an 11-year observation of a case of follicular lymphoma. The blood picture and the clinical signs were similar to those of acute leukemia at the beginning of illness. Within a few weeks these clinical symptoms disappeared; the blood became normal and has remained so for the ensuing 11 years. The interesting histological observations, together with the long duration of this case, are other unusual features.

REPORT OF CASE

R. S., a white man, was 29 years of age when first seen on May 8, 1940.

Present Illness.—He complained of (1) sore throat that made swallowing difficult; (2) tiredness; (3) fever; (4) enlarged lymph nodes.

Previous History.—He felt well until March, 1940, when he noticed a large node under his left armpit. He thought this was due to muscular strain from the heavy physical work he was performing. In April, 1940, his gums became swollen and painful and sore throat developed. When these conditions became worse at the end of April, he went to a dentist, who, recognizing the systemic nature of the sickness, advised the patient to seek medical examination.

Results of Physical Examination.—This well-developed, muscular young man appeared to be acutely ill. His temperature was 101.2 F. All his superficial lymph nodes were enlarged to a varying extent. The axillary lymph nodes on both the left and the right sides were greatly enlarged to about the size of a golf ball. Less enlarged were the cervical, submandibular, anterior and posterior auricular, occipital, and jugular nodes. The inguinal and femoral nodes were cherry-sized. All these nodes were discrete and not tender. The gums were swollen, red, and tender and bled easily. Stomatitis was present. The pharynx was red. The tonsils were bulging and red. On the left tonsil and at the upper pole of the right tonsil, necrotic ulcers were present. On the left, the ulcer was about the size of a pea; on the right, the ulcer was somewhat smaller. Both ulcers had sharply defined, dirty-grayish edges.

16. Saxén, E.: On Giant Follicular Lymphadenopathy, Acta path. et microbiol. scandinav. **26**:840-854, 1949.

17. Custer, R. P., and Bernhard, W. G.: The Interrelationship of Hodgkin's Disease and Other Lymphatic Tumors, Am. J. M. Sc. **216**:625-642 (Dec.) 1948 (see p. 641).

The chest and heart were found to be normal. The blood pressure was 130/80 mm. Hg, and the pulse rate, 102 and regular. The abdomen was soft; the liver and spleen were not enlarged. The extremities, save for the mentioned lymph nodes, were normal. Only normal reflexes could be elicited.

Laboratory Findings.—The blood count from the first examination showed 4,150,000 red cells and 42,000 white cells per cubic millimeter and 12.5 gm. of hemoglobin per 100 cc. The differential count revealed 8% segmented neutrophils; 17% normal lymphocytes, and 75% abnormal lymphocytes, most of them with notched or completely split nuclei. Results of this and subsequent white cell counts are tabulated in Figure 1. Sternal puncture was performed, the percentage proportions being tabulated with those of subsequent examinations in the table. Except for traces of albumin, the results of urinalysis were normal. The Kahn reaction was negative. The heterophile antibody test was performed three times and gave a negative reaction each time. The bleeding, clotting, and clot retraction times were normal. The thrombocyte

Differential Cell Counts in Aspirated Bone Marrow Specimens, from 1940 to 1949

	1940 (Sternal)	1943 (Sternal)	1947 (Sternal)	1949 (Iliac)
Myeloblast	..	1	1	1
Progranulocyte	1	1	2	2
Myelocytes				
Neutrophil	3	11	10	12
Eosinophil	1	1	2	1
Basophil	..	..	..	..
Metamyelocytes				
Neutrophil	..	20	24	20
Eosinophil	1	1	2	3
Basophil	..	..	..	1
Segmented cells				
Neutrophil	4	22	16	15
Eosinophil	..	2	2	2
Basophil	..	..	..	..
Rubriblast	1	..	1	1
Prorubricyte	..	1	1	1
Rubricyte	..	1	4	5
Metarubricyte	4	4	12	14
Megakaryoblast	..	..	..	..
Megakaryocyte	..	1	1	2
Monocyte	1	1	1	3
Plasma cell	..	1	1	1
Lymphocyte	23	23	17	14
Notched-nucleus cell	61	9	3	2

(platelet) count was 220,000, the control count being 240,000. The reaction to the tourniquet test was negative. Agglutination tests for Brucella, typhoid, and paratyphoid organisms gave negative reactions.

The sternal marrow was flooded with abnormal notched-nucleus cells (Fig. 2*A*). Every transition from slight or no indentation of the nucleus to complete separation into two halves could be observed. The blood picture showed 75% of these cells (Fig. 2*B*).

Our impression was acute leukemia. Some doubts arose, however, for two reasons: 1. The red blood cell count, hemoglobin concentration, and thrombocyte counts were normal at the first examination and showed only insignificant decreases during the days of observation. 2. The white blood cell count stayed at the level of about 40,000 and did not rise in the next few weeks.

To establish the diagnosis, the removal of one of the enlarged lymph nodes for biopsy was suggested to the patient. At that time he was feeling somewhat better and hesitated to undergo even such minor surgery. He was receiving local treatment for the oral lesions, acetylsalicylic acid in small divided doses, and vitamins. Although urged to remain, the patient left for Wisconsin to visit his father. In the following 10 to 14 days, his condition gradually improved. His fever disappeared; the gums slowly returned to normal; the soreness in the throat was gone. But he felt that his tonsils were still enlarged—as were the lymph nodes.

He rested until July, 1940, then returned to Chicago. Another blood count was performed on July 11, 1940, and the results were normal.

Subsequent Course.—During the following months he felt that his cervical lymph nodes became smaller but that other nodes and the tonsils were still large. In October, 1941, he consulted another physician, who performed a tonsillectomy. No histological examination was made. The patient was reassured that the other nodes would in time be dissolved "in a natural way." His general condition seemed much improved, and he began to work again, continuing to do so until August, 1943. At that time he returned to us with the complaint that his legs were tired.

Results of this physical examination compared with those of the first showed normal oropharyngeal findings. There was some change in the size of several of the enlarged lymph nodes. The cervical nodes had become smaller, whereas the inguinal and femoral ones had grown larger. A fist-sized mass was felt in the abdomen above the left inguinal ligament. The blood

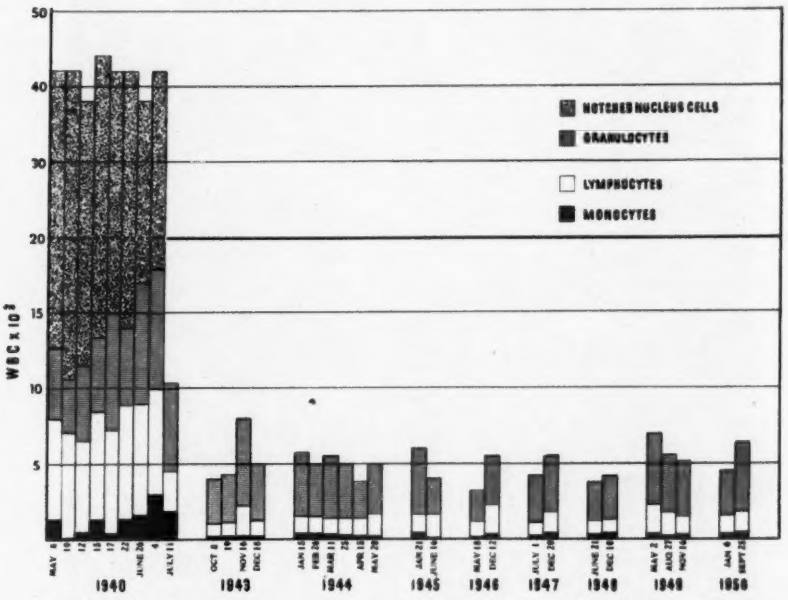

Fig. 1.—Patient's white blood cell counts and differential counts from May, 1940, to September, 1950. The last counts were performed in June, 1951, after the completion of this chart. These showed comparable results.

count showed mild leucopenia and lymphopenia but was otherwise normal. He refused biopsy until the end of September, when one day his entire left leg became edematous. He was hospitalized on Sept. 30, 1943, and Dr. John L. Keeley performed a biopsy of the right inguinal lymph nodes.

Roentgen examination of the chest and gastrointestinal tract revealed an essentially normal condition. A sternal puncture (second) showed normal marrow, except for a slight increase of lymphocytes and the presence of some of the notched-nucleus cells. Such cells, however, could not be found in the blood smears.

From Oct. 5 to 26, 1943, the patient was given four x-ray treatments to the anterior lower half of the abdomen, four treatments to the anterior upper half of the abdomen, three treatments to the left axilla, and four treatments to the right axilla. The factors employed were as follows:

200 kv., 25 ma., using 1 cm. Al plus 1 cm. Cu filtration, with 20 by 20 cm. portal at focus-skin distance, 65 cm., for a dose of 250 r, 11.5 minutes per dose. After these treatments, the mass in the abdomen disappeared entirely, and the axillary glands regressed almost completely.

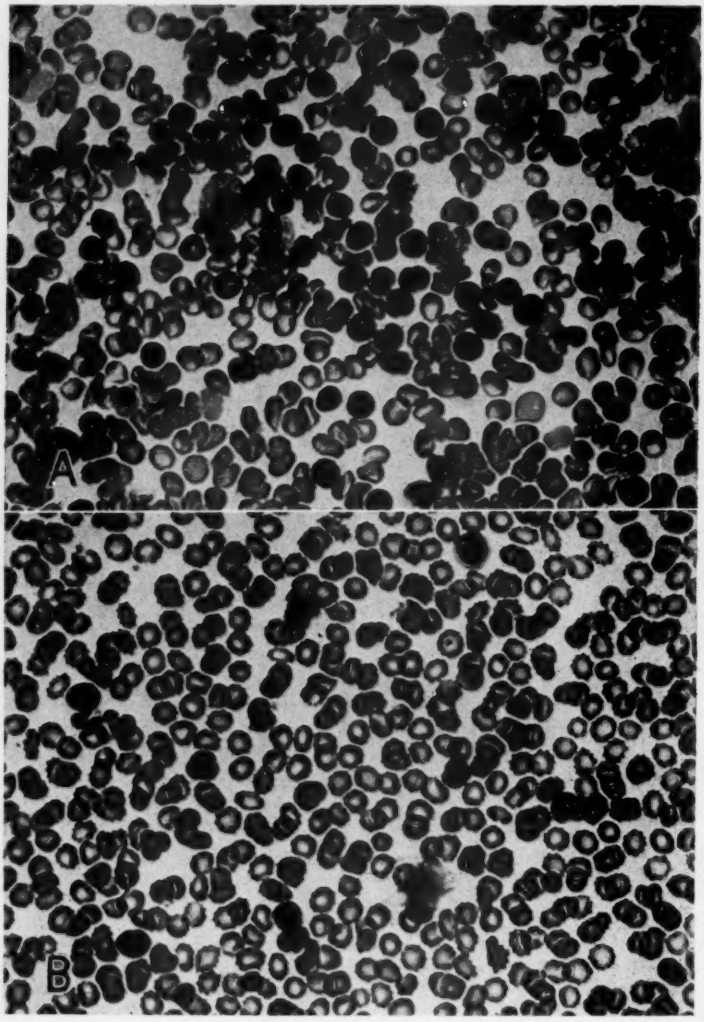

Fig. 2.—*A*, photomicrograph of aspirated sternal bone marrow (May 8, 1940). Wright's stain; × 550. Large numbers of notched-nucleus cells pervade the bone marrow and give the appearance of acute leukemia. In some cells the notch divides the nuclei completely into two or three lobes. *B*, blood film (May 8, 1940). Wright stain; × 550.

On Sept. 25, 1944, the patient returned. He stated that he was feeling well, but examination revealed enlargement of the nodes in both axillae and in the left femoral region. However, the nodes were not considered large enough to warrant further treatment at that time.

On Aug. 21, 1945, the patient came in complaining of dyspnea. Upon roentgen examination, involvement of the mediastinal lymph nodes was found (Fig. 3*A*). The axillary and the left inguinal nodes had increased in size since the previous visit. From Aug. 22 to Sept. 14, 1945, the patient was given six treatments to the anterior mediastinum, four treatments to the left anterior inguinal region, two treatments to the left axilla, and two treatments to the anterior left pelvis. The factors employed were 200 kv., 25 ma., using 1 mm. Cu plus 1 mm. Al filtration, in a field 15 by 20 cm., at focus-skin distance, 50 cm., 250 r. After these treatments, the dyspnea was relieved and the superficial nodes regressed almost completely. Roentgen examination showed the chest clear from the mediastinal tumor (Fig. 3*B*).

On Nov. 28, 1945, the patient reported that he was feeling well. There were small discrete nodes in the cervical and axillary regions. The right inguinal and right femoral nodes were moderately enlarged. There was no increase in the retromanubrial dulness. Again on Jan. 30 and Feb. 1, 1946, he was given two treatments of 250 r each to the left axilla. Except for the episode of the mediastinal tumor and the periods of treatment, the patient felt well and continued to work. In 1947 he had some difficulties with an inguinal hernia. This was operated on by Dr. J. L. Keeley. At the same time a lymph node biopsy, a sternal biopsy, and sternal puncture were performed. This sternal puncture showed findings similar to those of the second

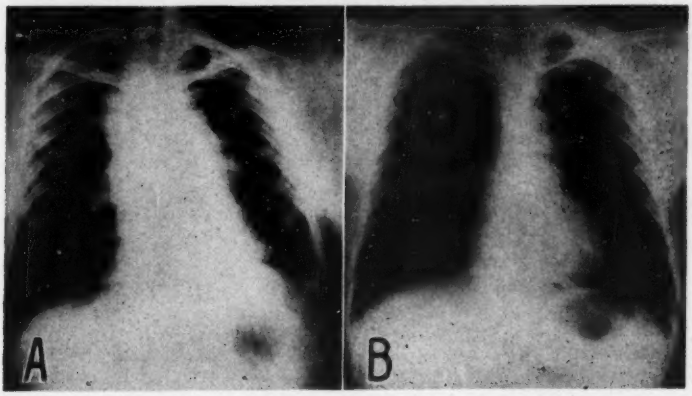

Fig. 3.—*A*, roentgenogram of the chest (Aug. 21, 1945) shows mediastinal tumor and the presence of some fluid in the left side of the chest. *B*, roentgenogram of chest after completion of irradiation therapy (October, 1945) shows regression of the tumor; the left costophrenic angle is also clear. Follow-up roentgenograms to date show the chest to be normal.

sternal puncture. Again, a few notched-nucleus cells were seen in the sternal marrow. No such cells were observed in the peripheral blood. Now the roentgen picture of the chest was normal.

The patient felt well and continued working until the summer of 1949. He had some teeth treated and noticed the appearance of several enlarged submandibular nodes. He thought these might have been caused by his tooth troubles. Biopsies of a submandibular lymph node and an iliac puncture were performed (Table).

From Aug. 2 to 26, 1949, the patient was given treatment to the submandibular region. The radiation factors employed were as follows: 200 kv., 25 ma., using 1 mm. Cu plus 1 mm. Al filtration, in a field 15 by 20 cm., at focus-skin distance, 50 cm., 300 r, 7.5 minutes per dose, 10 doses to the right and 10 to the left side of the neck, and from Aug. 22 to 26, 1949, 200 kv., 25 ma., using 1 mm. Cu plus 1 mm. Al filtration, in a field 10 by 10 cm., at focus-skin distance, 50 cm., 500 r, 12.5 minutes, 5 doses to the anterior right groin.

The patient is now 40 years of age. He resided and worked in Florida between 1947 and 1950 but came yearly to Chicago for examination.[18] At present the patient resides and works

18. Dr. Richard Reeser Jr. reported on blood smears made during the patient's stay in Florida.

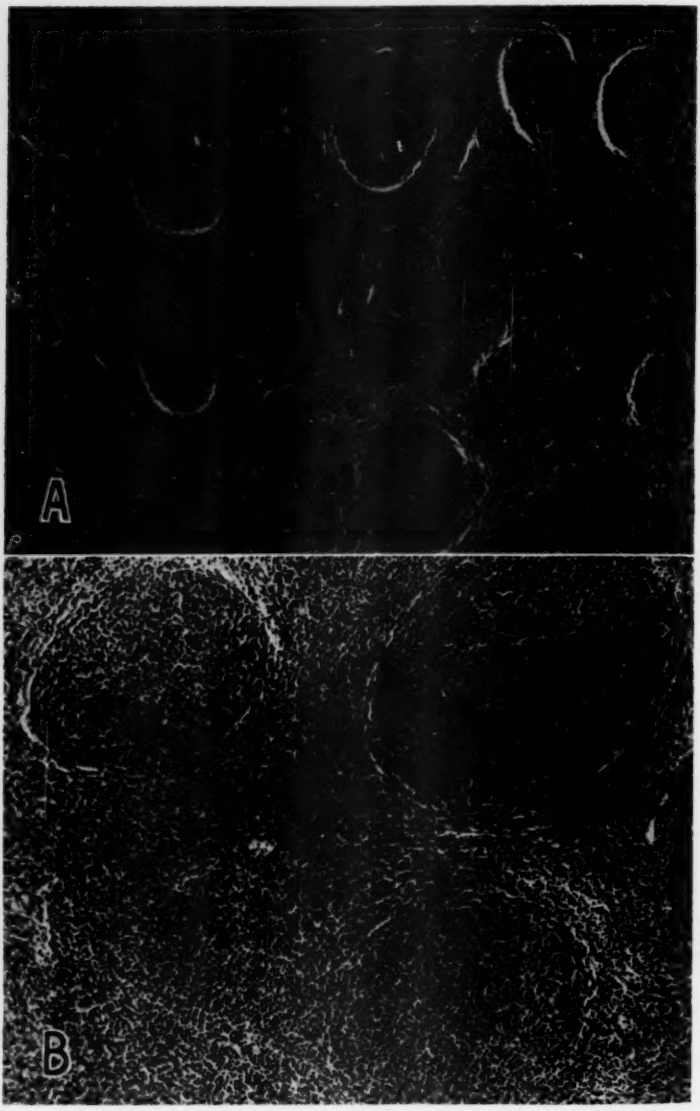

Fig. 4.—*A*, photomicrograph of inguinal lymph node biopsy specimen (Sept. 30, 1943). Some of the giant follicles are well defined; others blend with the cellular interfollicular tissue; × 30. *B*, higher magnification of same biopsy specimen, showing the uniformity of cells comprising the follicles; × 165.

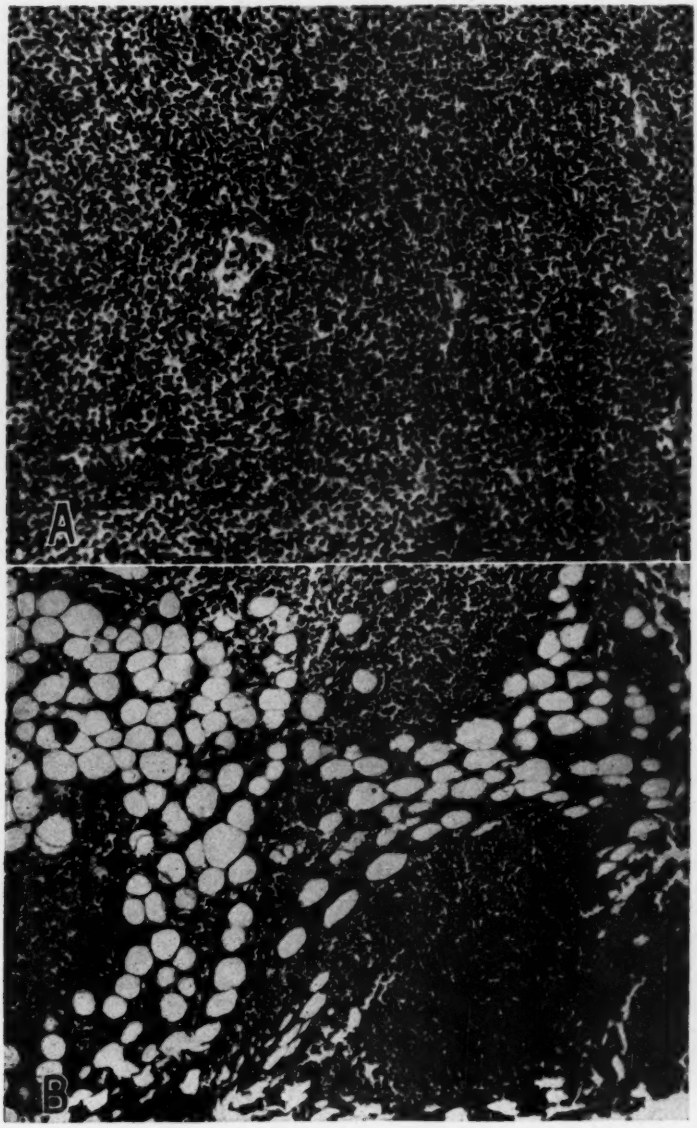

Fig. 5.—*A*, photomicrograph of another part of same biopsy specimen as in Figure 4. The appearance is that of reticulum-cell sarcoma; × 300. *B*, showing infiltration of the capsule of the lymph node with giant follicle formation; × 165.

in Chicago. He feels well and has no complaints. His last blood count (July, 1951) showed 5,100,000 red cells, 13.5 gm. of hemoglobin, and 4,500 white cells. Even though the white blood cell and differential counts are within normal limits, they always border on leucopenia and lymphopenia.

Histological Observations on Lymph Node Biopsy Specimens.—Credit for the conclusive histological diagnosis is due to Dr. Israel Davidsohn, who reviewed the different sections derived from three biopsy specimens taken in the years 1943, 1947, and 1949.

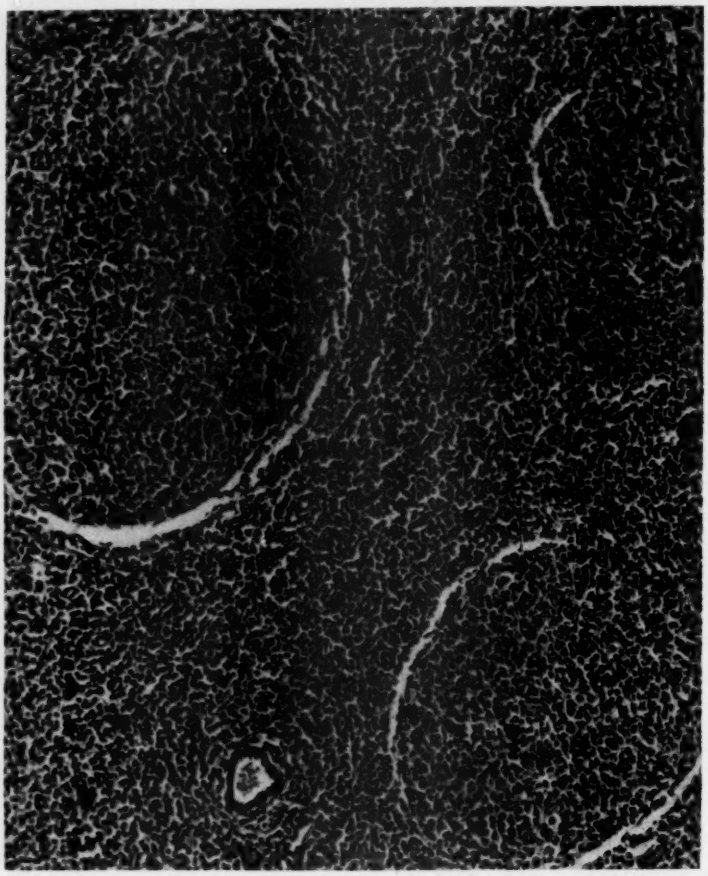

Fig. 6.—Photomicrograph of submandibular lymph node biopsy specimen (July 23, 1949). The structure is similar to that illustrated in Figure 4; × 300.

Sections of the first biopsy specimen (Sept. 30, 1943) revealed two different structures (Figs. 4 and 5*A*). One showed marked increase of the lymph follicles, which varied moderately in size. Some of the follicles showed a rather sharp line of demarcation from the adjacent pulp. Others were fused with the large numbers of cells between the follicles. The cells of the follicles were moderately irregular, with round, oval, or indented pale nuclei. Numerous mitotic figures could be seen. The tissue between the follicles showed somewhat increased vascularization.

Other sections disclosed complete loss of the follicular structure. Over wide areas fairly large-sized cells could be seen with scant cytoplasm and round, oval, or indented nuclei with numerous mitoses. The capsule was intact in places; elsewhere the tumor cells infiltrated into the capsule and adjacent fibroadipose tissue (Fig. 5*B*). These sections resembled lymphosarcoma of reticulum-cell origin.

Sections from the second biopsy specimen (an irradiated lymph node removed Nov. 28, 1947) showed the same giant follicular structure. The peripheral mantle of lymphocytes around the germinal center was lacking, and there was a considerable dense fibrosis. The central aspect of the nodes revealed strands of mature lymphocytes in heavy fibrous tissue.

The sections of the third biopsy specimen (July 23, 1949) were identical with the giant follicle structure of the first biopsy specimen (Fig. 6). Silver impregnations showed slight distortion and density between the follicles, as observed by Gall and associates.[3] In some places the argentophil fibers appeared to be normal; in others, broken-up fibrils could be seen.

COMMENT

A. *The Clinical Course.*—It is remarkable that each stage of this patient's illness when viewed separately has malignant characteristics. Such stages were the transient leukemic blood picture and clinical features; the sudden, massive edema of one leg due to pressure of lymph nodes; the formation of a mediastinal tumor, and the recurrent enlargement of different groups of superficial and deep lymph nodes.

On the other hand, if one views the entire course of the disease rather than the single stages, it appears to be benign. The leukemic features disappeared spontaneously. The other difficulties arose at intervals over a period of years and always caused only local disturbances, never general systemic symptoms, such as fever, anemia, or anorexia. Each time the condition responded excellently to x-ray treatment. Shortly after treatment was completed, the patient returned to his physical work. The clinical course is not that of one prolonged illness interrupted by short phases of good health. Rather the patient has enjoyed good health and has worked during the past 11 years, except for three short periods of sickness and treatment.

B. *Histological Structures.*—The histological structure of the lymph nodes has remained the same throughout the 11 years of observation. It appears that this structure is similar to that described by Symmers[14] as "polymorphous cell sarcoma" and by Gall and associates[3] as "Type III" in their classification of follicular lymphomas. The similarity of some of the microscopic fields to reticulum-cell sarcoma is striking.

In the first lymph node biopsy, sections of two different parts of the same specimen revealed two different structures. One showed the structure of reticulum-cell sarcoma; the other, the characteristic structure of follicular lymphoma with sarcomatous changes. The coexistence of different histological structures in lymphatic tumors was excellently demonstrated recently by Custer and Bernhard.[17] In our case the follicular structure predominated in the later biopsy specimens.

The large follicular pattern was invariably associated with an infiltration of the capsule, resulting in a matted-together appearance of the removed nodes. Such a tendency to invade the capsule has been emphasized by Baehr and Klemperer.[13]

C. *The "Notched-Nucleus Cells."*—In our case large numbers of the tumor cells in the sternal marrow and blood were characterized by notched nuclei. Such

cells were first described by Isaacs [19] in 1939. He found these cells present in cases of acute and subacute leukemia.

The notch of the nucleus in our case gradually cuts in deeper, eventually separating the nucleus into two halves. Sometimes a third lobe is formed.

The number of notched-nucleus cells is less spectacular in the lymph node sections, the first of which was examined two and a half years after the leukemic features disappeared. Here and there these sections show notched, indented, or severed nuclei. It is possible that more of these notched cells would have been found in the lymph nodes at the time of the blood invasion.

D. *Follicular Lymphoma and Leukemia.*—From the literature it is obvious that follicular lymphoma may be associated with aleukemic or frank lymphatic leukemia. In the cases reported in the literature the leukemic features appeared late in the disease and persisted until the patient's death.

In our case the clinical symptoms and the blood and bone marrow findings characteristic of leukemia appeared for only two to three months at the onset and then disappeared spontaneously. Such cases have not previously been published in connection with follicular lymphoma. However, they apparently are not rare in the lymphosarcoma group. Gall and Mallory state (p. 402)[8]:

> Fifty patients who exhibited some phase of leukemia during their course were selected for analysis on the basis that two or more blood studies were recorded at extended intervals during their disease. Of these, 13 patients were non-leukemic when first observed but developed leukemia later in the course, six were leukemic at the initial observation but showed normal blood pictures prior to death and two other patients were leukemic at the beginning and at the end of the disease but were non-leukemic in the interval. Forty-two per cent of this group, then, exhibited marked relapse into, or remission from, leukemia. An additional 38 per cent showed a variety of shifts among the aleukemic, subleukemic and leukemic phases without reverting to normal. In only 20 per cent of the 50 patients was the blood picture entirely constant throughout the course of the disease.

Similar observations regarding the white cell count were made by Hellwig [20] on 130 cases of malignant lymphoma and by Custer and Bernhard [17] on 1,300 lymphatic tumors.

All these authors, however, leave such challenging facts as these unaccounted for: 1. Not every lymphoma is accompanied with a leukemic blood picture. 2. Once the tumor cells enter the circulation, they do not in every case flood the blood stream, causing a fatal ending with acute leukemia. Their number may vary at times, giving an "aleukemic" or "subleukemic" blood picture. In the same patient their number may vary from time to time.

In the literature attempts can be found to explain the pathological mechanism which enables the tumor cells to enter the circulation. Such explanations are as follows:

1. Lymphosarcoma cells break into the blood stream by infiltrating the wall of some veins (Benda).[21] This supposition was refuted by Sternberg,[22] who pointed

19. Isaacs, R.: "Notched Nucleus Cell" Leukemia, Proc. Central Soc. Clin. Research **12**:37 (Oct.) 1939.

20. Hellwig, C. A.: The Value of Radical Surgery in Selected Cases, Surg., Gynec. & Obst. **84**:950-958 (May) 1947.

21. Benda, C.: Anatomische Mitteilungen über akute Leukämie, Verhandl. Kong. inn. Med. **15**:371-382, 1897.

22. Sternberg, C.: Über lymphatische Leukämie, Ztschr. Heilk. **25**:201-246, 1904.

out that in those cases of lymphosarcoma in which the blood is normal, such an invasion of the blood vessels is the most marked.

2. The tumor cells get into the circulation by infiltrating moving organs, such as the lungs (Isaacs).[23] This interesting view can be challenged on the basis of the many cases in which lymphosarcoma does not involve the lungs and still the blood shows leukemic features. On the other hand, many lymphosarcoma cases with pulmonary metastases do not show deviation from the normal blood picture.

3. The tumor cells get into the circulation as an effect of x-ray irradiation (Kato and Brunschwig).[24] Undoubtedly, there are rather impressive cases in which the sudden appearance of a terminal lymphosarcoma-cell leukemia appears immediately after x-ray treatment was begun for lymphosarcoma. However, the number of such lymphosarcoma cases must be rather small compared with those large numbers under treatment without development of leukemic features.

4. The tumor cells get into the circulation through infiltration of the bone marrow.[25] To accept this view, one would have to suppose that the tumor cells cannot enter the circulation from the infiltrated lymph nodes but only through the bone marrow. Infiltration of the bone marrow is certainly a usual finding in a leukemic blood picture. However, the opposite is equally true. The bone marrow shows presence of tumor cells in many lymphosarcoma cases with a normal blood picture.[26]

In our case the well-marked notched-nucleus cells were present in large numbers, in both sternal bone marrow and blood. These cells disappeared spontaneously from the blood, while their numbers only decreased but did not disappear from the bone marrow. In this respect, one of Wiseman's [27] cases was also instructive. The sternal bone marrow in this case contained large numbers of lymphosarcoma cells all the time, whereas the peripheral blood on occasions was entirely free from these cells.

Such cases demonstrate that infiltration of the bone marrow is not the decisive factor in the invasion of the blood stream with lymphosarcoma cells.

5. Gall and Mallory [8] emphasized that ". . . no constant histologic substrate permits one to predict whether or not the blood picture will prove 'leukemic'."

These views consider only the possible mechanisms by which tumor cells find their way into the circulation.

Little, if any, attention has been given thus far to other possible factors. In this respect a case of Isaacs [28] is of special significance. The patient was a 31-year-old woman with lymphosarcoma-cell leukemia. The patient's blood picture, although leukemic before and after, became normal during pregnancy. Such a case would

23. Isaacs, R.: The Physiologic Histology of Bone Marrow, Folia haemat. **40**:395-405 (March) 1930.

24. Kato, K., and Brunschwig, A.: Acute Leukemia Following Lymphosarcoma, Arch. Int. Med. **51**:77-89 (Jan.) 1933.

25. Türk, W.: Ein System der Lymphomatosen, Wien. klin. Wchnschr. **16**:1073-1085 (Sept. 24) 1903. Evans, W. A., and Leucutia, T.: The Neoplastic Nature of Lymphatic Leucemia and Its Relation to Lymphosarcoma, Am. J. Roentgenol. **15**:497-513 (June) 1926.

26. Cooper and Watkins.[10] MacCallum, W. G.: A Textbook of Pathology, Ed. 7, Philadelphia, W. B. Saunders Company, 1940, p. 909.

27. Wiseman, B. K.: Lymphatic Leukemia, J. A. M. A. **118**:100-105 (Jan. 10) 1942.

28. Isaacs, R.: Lymphosarcoma Cell Leukemia, Ann. Int. Med. **11**:657-662 (Oct.) 1937.

point to the possibility of hormonal influences. Observations [29] concerning the effect of corticotropin (ACTH) on the white blood cells encourage such a trend of thought. Other possibilities were pointed out by the work of Steinberg and Martin.[30] Study of a possible humoral factor in the regulation of circulating tumor cells appears to be promising.

SUMMARY

A case of follicular lymphoma, so far of 11 years' duration, is reported. The clinical blood and bone marrow findings showed leukemic features for about three months at the beginning of the disease 11 years ago. The tumor cells were characterized by notched nuclei. The blood has been normal ever since, with persistent leucopenia and lymphopenia, in spite of the fact that the bone marrow has always contained some of the tumor cells. On three occasions at broad intervals lymph node enlargements required x-ray treatment, to which there was always excellent response. The pathological mechanism through which tumor cells enter the blood stream is discussed, and the possibility of humoral factors is emphasized.

29. Hills, A. G.; Forsham, P. H., and Finch, C. A.: Changes in Circulating Leukocytes Induced by the Administration of Pituitary Adrenocorticotrophic Hormone (ACTH) in Man, Blood **3**:755-768 (July) 1948.

30. Steinberg, B., and Martin, R. C.: Leukoagglutination Differentiation of Normal Leukocytic and Leukemic Cell-Type, J. Immunol. **52**:71-75 (Jan.) 1946.

Progress in Internal Medicine

THE RATIONALE AND CLINICAL USE OF STEROID HORMONES IN CANCER

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HAVERSTRAW, N. Y.

I. INTRODUCTION AND BACKGROUND

A. The Cancer Problem and Its Association with Hormones

A hundred years ago, when the average life expectancy was 34 years, death from cancer was a remote possibility. Today, when the life expectancy is about 64 years and increasing, cancer is an ever-present menace, since it is commonest in the older age groups (Ackerman and del Regato). In 1940 there were 170,000 deaths from cancer in the United States, thus making cancer second only to diseases of the circulatory system as a major cause of death. About 18% of all males and 22% of all females can be expected to harbor a cancer of some type during their lifetime (Dorn).

Within recent years there has been a marked increase in cancer research directed toward the development of chemotherapeutic agents. The stimulus for these studies has been provided by the recognition of the limitations of surgery and irradiation in therapy and the need for cancer control. One of the better means of approach is the study of carcinogenic substances, for knowledge of carcinogenesis may show the feasibility of reversal of that process (Karnofsky). A carcinogen may be defined as a substance whose application under certain conditions is followed by the occurrence of tumors that otherwise would not have appeared (Gardner, 1944).

The chemical similarity of carcinogenic hydrocarbons, such as methylcholanthrene, to cholesterol and the steroid hormones (Fig. 1) drew attention to the possibility of a perversion in the steroid metabolism with production of an endogenous carcinogen. Estrogen could theoretically be converted to a carcinogenic cholanthrene by preliminary passage through a 3-desoxyequilenin stage (Pincus and Thimann). It is significant that the estrogenic steroid hormones, probably derived from cholesterol, a constituent of every living cell, can induce malignant growth in certain strains and species of animals (Berrill; Gardner, 1944, 1947). In mice, the most frequently used experimental animals, tumors of the mammary gland, uterine cervix, testis, lymphoid tissue, bone, and pituitary have been produced by estrogen administration (Burrows, 1945; Gardner, 1944, 1947). Since synthetic estrogens, unrelated in chemical structure, may also produce these effects (Gardner, 1947; Perry and others; Robson and Bonser; Shimkin and Grady), it has been postulated that physiologic overstimulation of the tissues may result in an occasional chromosome mutation producing malignant behavior of the cell (Berrill).

Furthermore, changes in hormonal relationships in mice by castration can produce adrenal tumors (Woolley and Little) and ovarian tumors in splenic transplants (Li and Gardner). Other disturbances that result in hormonal imbalance

First Prize Winner, Schering Award 1950.

involve the rate of production, destruction, and utilization of the hormone (Gardner, 1948), the quality of the hormone produced (inherited carcinogenicity?) (American Association for Cancer Research, 1946; Kennaway and Kennaway; F. Smith), the sensitivity of the end-organ, and the duration of the stimulus (implicated by some authors in endometrial carcinoma: Novak and Yui; C. L. Randall; Speert, 1948).

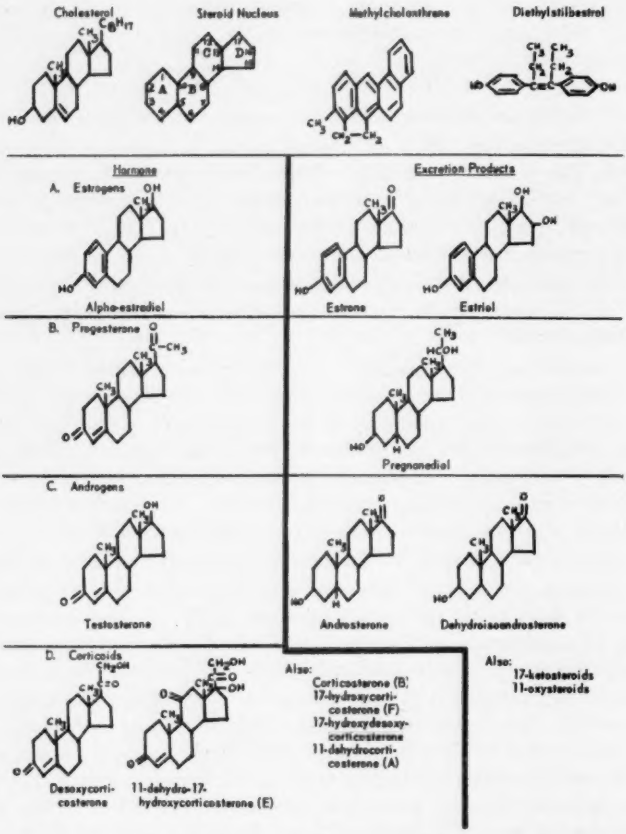


Fig. 1.—Chemical formulas of steroid hormones and excretion products.

The cancer cell in certain instances may still be under the influence of hormonal factors affecting growth. Hormonal alteration therapy by means of castration, as in prostatic carcinoma (Huggins, 1949) or with the administration of steroid hormones (Adair and others, 1949; Nathanson, 1944*a*), can favorably influence the course of the disease in these cases.

Therefore, the association of hormonal factors in the production and progression of cancer in these organs requires a review of the basic endocrine relationships and steroid-hormone properties, so that a sound rationale for the use of steroid hormone

therapy may be evolved. Furthermore, careful examination of pertinent laboratory studies is helpful in providing suggestions for future therapy and substantiation of the clinical reports.

B. Endocrine Interrelationships (Fig. 2)

The basic postulates of sex-hormone relationships were formulated in 1932 (C. R. Moore and Price) and are applicable with several modifications and additions.

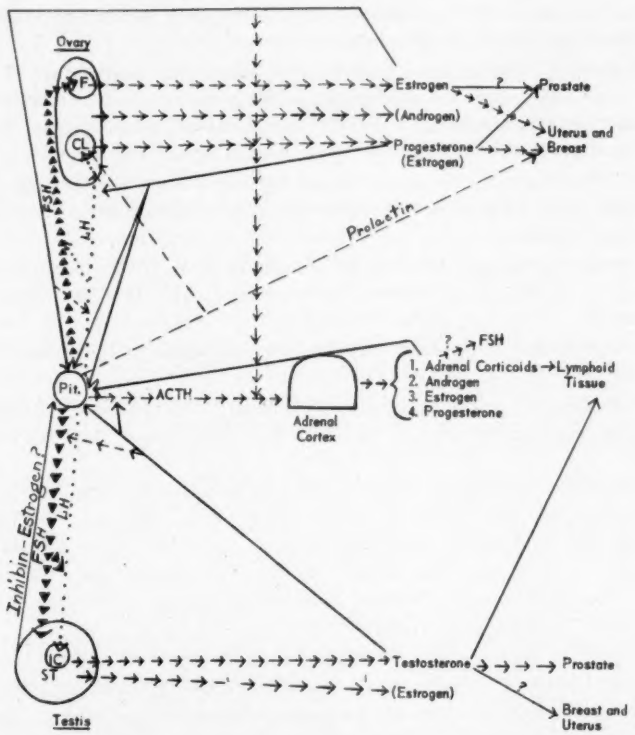


Fig. 2.—Endocrine interrelationships. Estrogen, androgen, progesterone, testosterone, and corticotropin (ACTH) stimulation is indicated by arrows. Hormonal inhibition is indicated by solid lines. Prolactin stimulation is indicated by dashes. Follicle-stimulating-hormone (*FSH*) stimulation is indicated by lines of triangles. Lutein-hormone (*LH*) stimulation is indicated by lines of dots. Questionable direct inhibition and questionable stimulation are indicated by question marks over solid lines and over lines of arrows, respectively. Lines of arrows and dashes indicate inhibition or stimulation dependent on dosage. *F* means follicles; *Pit.*, pituitary; *CL*, corpus luteum; *IC*, interstitial cells, and *ST*, seminiferous tubules.

1. *Anterior Pituitary Secretions.*—Secretions produced by the anterior lobe of the pituitary gland (gonadotropins) stimulate the gonads to produce germ cells and sex hormones. The gonadotropins are lipid soluble, thermolabile, and closely associated with a protein molecule (Harrow). They include the following hormones (Best and Taylor; Burrows, 1945; Harrow; Lloyd; Pincus and Thimann; Rakoff):

a. Follicle-Stimulating Hormone: Follicle-stimulating hormone (F. S. H.) influences the maturation and function of the ovarian follicle in the female and the seminiferous tubules of the testis in the male.

b. Luteinizing Hormone: Luteinizing hormone (L. H.) aids F. S. H. in the production of female sex hormone (estrogen) by the follicle and stimulates the formation of the corpus luteum. In the male it influences the production of the male sex hormone (androgen) by the interstitial cells of the testis. F. S. H. appears to act synergistically in increasing the androgen production when it is administered in association with L. H. A small amount of androgen is secreted normally by the ovary, but the exact site of origin is not known.

c. Prolactin: Prolactin has attained prominence within recent years as another gonadotropin essential for the maintenance of the corpus luteum, with production of the second female sex hormone (progesterone) as well as some estrogen. The function of prolactin in the male has not as yet been established.

2. *Effect of Gonad Hormones.*—Gonad hormones exert a depressing effect on the anterior lobe of the pituitary, which results in a diminution in the amount of gonadotropin produced.

a. Estrogen: Estrogen inhibits the production of F. S. H. Small doses may stimulate L. H. release, while large doses inhibit L. H. (Best and Taylor; Burrows, 1945).

b. Progesterone: Progesterone inhibits the production of L. H. and F. S. H. (Burrows, 1945).

c. Androgen: Androgen (testosterone) inhibits L. H. production and may have a minor inhibitory effect on F. S. H. (Burrows, 1945; Lloyd; Salmon; Shorr and others).

d. "Inhibin": The role of a second hormone from the testis has not been definitely determined. It has been postulated that a tubular hormone, "inhibin," may act in the male to decrease the production of F. S. H. However, a small amount of estrogen is produced in the testis by the Sertoli cells and thus could act in the same fashion (Berthrong and others; Huggins and Moulder; Teilum). Therefore, the status of "inhibin" is still questionable.

3. *Effect on Reproductive Organs.*—Gonad hormones stimulate homologous reproductive accessory organs but do not affect heterologous accessories.

a. Female Reproductive Organs: Estrogen and progesterone influence the formation and normal function of female reproductive organs. Estrogen induces a proliferative phase in the endometrium and duct growth in the breast. Progesterone induces the secretory changes of the endometrium and breast acinar growth (Best and Taylor; Burrows, 1945).

b. Male Reproductive Organs: Testosterone stimulates the normal growth and function of the male reproductive organs, including the prostate gland (Best and Taylor; Burrows, 1945). It is extremely difficult to determine whether the sex hormones have specific actions upon the heterologous acccessories because of the possible indirect action by means of pituitary inhibition.

c. Effect of Estrogen and Progesterone: Estrogen and progesterone are believed to stimulate the growth of the anterior and middle lobes of the prostate, but it has been argued that these particular lobes are ambisexual. It is possible, but not

proved, that estrogens have a specific inhibiting effect upon the posterior lobe, which is purely a male organ (Huggins and Webster). However, estrogens may have a testosterone-neutralizing effect locally in the tissue (Pincus and Thimann).

d. Effect of Testosterone: Testosterone has been claimed to possess estrogenic and progesteronal properties to a minor degree (Salmon). However, a specific neutralizing action by testosterone on estrogen-stimulated tissue has also been demonstrated (Pincus and Thimann; Robson; Shorr and others), while variable effects of stimulation or inhibition have been produced in animal breast tissue depending on the species and dose (Burrows, 1945). In man, testosterone is believed to inhibit breast growth and lactation (Pincus and Thimann). Further evidence is needed before definite conclusions can be made.

4. *Gonad Hormones Have No Direct Effect on the Gonads of Either the Same or the Opposite Sex* (C. R. Moore and Price).—Evaluation of this postulate is again complicated by the indirect action of the sex hormones on the gonads, mediated through the action on the pituitary.

5. *Adrenocortical Hormone.*—The adrenal cortex is another source of steroid-hormone production and must be considered in regard to endocrine interrelationships because of its recent implication in the cancer problem (Huggins and Scott; Pearson and others, 1949; F. Smith).

a. Corticotropin Effects: The adrenocorticotropic hormone (corticotropin; ACTH) from the pituitary stimulates the growth and function of the adrenal cortex (Best and Taylor; Burrows, 1945; Tepperman and Tepperman; Sprague). It is not certain whether corticotropin is able to cause the production of all the cortical hormones (Fig. 1) or of just those produced in a certain zone (Tepperman and Tepperman). There is reason to believe that corticosterone and its closest allies are formed in the outer zones, while the sexual hormones (androgen, estrogen, progesterone) are produced nearer the medulla (Burrows, 1945; Tepperman and Tepperman) from tissue capable of undergoing changes in its aspect according to the period of life considered. It may substitute as the male or female gonad before or after the gonad's span of activity (Llusia).

This area has been called the X-zone; it was first described in human adrenal glands during early life and then was found and studied in mice. In male mice this zone disappears by the sixth week of life, but in female mice it may persist for a considerable time (Burrows, 1936). Castration or estrogen administration in male mice before maturity leads to persistence of the X-zone, while after maturity the X-zone may reappear (Burrows, 1936; Parkes). Administration of androgen causes disappearance of the X-zone in castrated males and intact female mice (Parkes). These effects may be mediated through the action of the sex hormones on corticotropin.

b. Corticotropin Inhibition: In both sexes, testosterone and progesterone are believed to be inhibitors of corticotropin, while estrogen may stimulate corticotropin production (Burrows, 1936; Lloyd; Tepperman and Tepperman).

c. Effect of Pituitary: There is a reciprocal relationship between the pituitary and adrenal glands, with the result that adrenal cortical secretions inhibit the production of corticotropin (Tepperman and Tepperman; Sprague). The depressing effect of adrenalectomy on the gonads is possibly due to the loss of general health (Parkes; Sprague) or occurs because the adrenal corticoids may stimulate F. S. H. production (Burrows, 1945; Thorn and others).

C. The Steroid Hormones (Fig. 1)

The steroid hormones (Best and Taylor; Burrows, 1945; Harrow; Pincus and Thimann) have been obtained in a pure form; therefore, their molecular structure is known. They all have a steroid nucleus with a methyl group on carbon 13. Differences in their hormonal effects depend on changes in saturation of ring A and added groups (Best and Taylor; Harrow; Pincus and Thimann). Cholesterol may be the ultimate source of the steroids (Pincus and Thimann). These hormones are lipid soluble and can be divided into four groups:

1. *Estrogens.*—Estrogens are called ovarian hormones but are also formed in the placenta, testis, and adrenal cortex (Burrows, 1945; Pincus and Thimann). Their properties depend upon an unsaturated ring A and a hydroxyl group on carbon 13. All members of this group exert stimulating effects upon the female sex organs, induce the secondary sex characteristics of the female, and have systemic effects of sodium, calcium, and phosphorus retention (Parkes). Their metabolism involves the conversion of alpha-estradiol, produced in the ovarian follicle, stroma, and corpus luteum, into estrone and estriol, the less active excretion products (Stimmel and May).

$$\text{Alpha-Estradiol} \rightleftarrows \text{Estrone} \rightarrow \text{Estriol}$$

The liver inactivates estrogen, and vitamin B complex appears to be related to the hepatic capacity for performing this function (Pincus and Thimann; Segaloff and Segaloff; Tagnon and Trunnell; Twombly and Taylor). The potency of the estrogens can be increased by esterification to form products such as estradiol benzoate or dipropionate. Ethinyl estradiol is a potent compound, but it is not converted into a natural estrogen by normal metabolism; thus, its estrogenic activity is probably inherent in the preparation itself (Stimmel and May). Synthetic compounds, such as diethylstilbestrol, have different chemical structures but similar estrogenic properties. Individual estrogen compounds may be administered by intramuscular and/or oral routes (Council on Pharmacy and Chemistry, 1947, 1949, 1951) or in subcutaneous pellet implants (Colston; Okie and others).

2. *Progesterone.*—Progesterone is called the corpus-luteum hormone, but it is also produced by the placenta and adrenal cortex (Burrows, 1945; Pincus and Thimann). Its properties depend upon a point of unsaturation between carbons 4 and 5, a keto group on carbon 3, and a methyl group on carbon 10. Progesterone produces modifying effects upon the female sex organs, conserves sodium and chloride, and facilitates the excretion of potassium (Burrows, 1945). Its excretion product is the inactive pregnanediol, and the site of metabolic conversion may be the liver (Lipschutz and others; Pincus and Thimann). Progesterone is administered intramuscularly or by subcutaneous pellets (Loesser; Trunnell and others). A product that may be taken by mouth is anhydrohydroxyprogesterone (Trunnell and others).

3. *Androgens.*—Androgens are considered testicular hormones, but they are also derived from the adrenal cortex, ovary, and possibly the placenta (Burrows, 1945; Pincus and Thimann). The molecular structure of testosterone, the most active androgen, is similar to that of progesterone, and the differing properties are due to various additions to carbon 17. Androgens stimulate the growth and function of the secondary sex organs in the male and induce the masculine secondary sex characteristics. Furthermore, testosterone has systemic properties that include

the retention of water and sodium (Parkes), thymic regression (Pincus and Thimann), and protein anabolism with nitrogen retention (Abels and others; Albright; Kenyon and others; Reifenstein and Albright). Its metabolic excretion products, androsterone and dehydroisoandrosterone, are weak androgens and have the 17-ketosteroid structure. Testosterone is inactivated in the liver (Lipschutz and others; Pincus and Thimann). Testosterone potency can be increased by esterification to form products such as testosterone propionate for intramuscular and pellet administration (Adair, 1949*b*; Prudente, 1945). In addition, testosterone can be given orally as a product formed by methylation on carbon 17 to produce methyltestosterone (Boger). Another compound, methylandrostenediol, is being tested. It has about 50% of the protein anabolic effect of testosterone, with almost no virilizing effects. It may be administered orally, intramuscularly, or by pellet implantation (Henderson and Weinberg; Homburger and others).

4. *Adrenal Cortical Hormones.*—The adrenal cortex secretes its own steroid hormones (corticoids) in addition to the sex hormones (Burrows, 1945; Llusia; Pincus and Thimann). The corticoids have a structure similar to that of progesterone and testosterone, but their properties are derived from differing structures on carbon 11 and 17. They include six compounds of known molecular structure and an active amorphous fraction. Desoxycorticosterone, without an alteration on carbon 11, has the property of maintaining fluid and electrolyte balance and is thus essential for life. Corticosterone, dehydrocorticosterone, and progesterone are less effective in this regard (Kenyon; Parkes). The compounds with a ketonic or alcoholic structure on carbon 11 (11-dehydrocorticosterone [compound A]; corticosterone [compound B]; cortisone [compound E], and 17-hydroxycorticosterone [compound F]) compounds have a strong action in gluconeogenesis (Kenyon). Cortisone and 17-hydroxycorticosterone, with hydroxyl groups on carbon 17, have a marked effect on producing lymphoid regression and eosinopenia (Kenyon; Pearson and others, 1949; Sprague) with increased circulating erythrocytes and neutrophiles (Thorn and others). With prolonged administration of these hormones, there is loss of sodium, chloride, potassium, calcium, phosphorus, and nitrogen, indicating the catabolic nature of the adrenal corticoids (Thorn and others). The excretion products of the cortical hormones are 11-oxysteroids and 17-ketosteroids, which can be determined quantitatively in the urine (Dobriner and others, 1943, 1947; Lieberman and others). Therapeutically, these hormones are administered indirectly by the injection of corticotropin for adrenal cortex stimulation or directly by use of adrenal cortical extracts and cortisone. There are several corticotropin preparations for intramuscular injection derived from animal pituitary glands, most of which contain a protein molecule of 23,000 units (Thorn and others). However, the active portion may be a smaller, dialyzable, heat-stable molecule (Astwood and others). A newer method of extracting it from hog pituitary glands has produced a greater yield of a more potent preparation (Astwood and others). Cortisone is prepared by partial synthesis from bile acids and is administered intramuscularly as cortisone acetate in saline solution. This preparation is slowly absorbed and has a prolonged action which extends over 24 hours, thus producing a cumulative effect (Thorn and others). Subcutaneous implantation of cortisone acetate pellets and oral administration are also being used, particularly for maintenance therapy (M. C. Rosenthal and others; Thorn and others).

II. EXPERIMENTAL AND CLINICAL RESEARCH

A. Female Breast Cancer

1. *Extent of the Problem.*—Although surgical treatment and irradiation therapy are the primary hopes for cure of breast carcinoma, the importance of palliation in this disease cannot be overemphasized. This is evident from the following facts:

a. High Incidence: Breast carcinoma is the commonest neoplasm in human beings, with an estimated 70,000 cases currently present in the United States (Ackerman and del Regato; McDonald and Guiss). About 26% of cancers in females originate in the breast (Ackerman and del Regato; Dorn; Fitts), and 4% of all adult women acquire this neoplasm (Chase; DeCourcy). More than 15,000 women die annually of the disease (Chase).

b. Frequent Failure of Cure by Surgical Treatment and Irradiation: Studies of five-year end-results revealed that 61 to 89% of the patients without axillary metastases survived, while only 21 to 34% of those with axillary metastases survivid. There was an over-all average of 36 to 50% survival in both groups (Adair, 1943, 1949*b*; Haagensen and Stout, 1942; Hopkins and Egnatz; Marshall and Hare; Nicolson and Grady). These figures are certainly an improvement over the five-year survival rate of 22% in untreated patients (Daland; Panel on Tumors; Wade) but leave much to be desired. Irradiation therapy alone resulted in 24 to 26% salvage (Adair, 1943, 1949*b*; Panel on Tumors; Wade), very little, if any, advantage in five-year survival. It is estimated that 50% or more of patients with breast cancer are treated too late for possible cure (McDonald and Guiss), and local recurrences take place in 8 to 22.8% with or without postoperative irradiation (Haagensen and Stout, 1942; Nicolson and Grady). Suggestions have been put forth for making the criteria of operability more stringent, thus raising the cure rate for surgical treatment and placing more patients in the palliative group (Haagensen and Stout, 1943). However, by these rules, a certain few patients would lose their opportunity for possible cure (Hopkins and Egnatz) and, therefore, the decision on the individual case rests with the surgeon.

c. Long Periods of Suffering: For each woman who dies of cancer of the breast, there are five living patients (Ackerman and del Regato) because of the cancer's relatively prolonged process of causing death in comparison with other cancers (Dorn; Nicolson and Grady). The average duration of life in the untreated patient from the first symptom is 40 months, and the mean duration is 30 to 39 months (Daland; Nathanson and Welch; Wade). When metastases involve all the axillary nodes, the average survival is 26 months (Chase).

Therefore, hormonal alteration as brought about by particular steroid hormone therapy is a needed palliative measure in breast cancer and is a step forward in the ultimate goal of chemotherapy for malignant disease (Council on Pharmacy and Chemistry, 1947, 1949, 1951; McCullagh). Furthermore, this treatment offers objective as well as subjective improvement in some patients and may prolong their useful life (Adair and others, 1949; McCullagh; McDonald and Guiss; Nathanson, 1950).

2. *Early Clinical Approach.*—The intricate interrelationship of the sex hormones and breast cancer has been investigated extensively by experimental and clinical methods, in order to provide a rational basis for steroid-hormone therapy. The concept of influencing breast carcinoma by endocrine alteration is not new.

Schinzinger in 1889 suggested oophorectomy as the means of hastening menopause, since he had noted that breast cancer was more rapidly fatal in young women. Beatson, in 1896, believed that abnormal function of the ovaries might be involved in the occurrence of breast carcinoma and was the first to perform oophorectomy for this disease, with improvement in three patients. Other surgeons in the early 1900's reported similar favorable results, ranging from 25 to 40% improvement following ovariectomy (Boyd; Lett and others; Thomson). When patients over 51 years old were excluded, the improvement rate rose by 15% (Lett and others). However, the surgical approach entailed a 6% mortality rate at that time (Lett and others), and, after Halberstaedter and Hochman demonstrated that sterilization could be produced by x-rays in 1905, this method began to supplant surgical castration. Irradiation castration was first used in treatment of mammary carcinoma by de Courmelles (cited by F. Smith) in 1909, and Wintz was so convinced of its value that he used it routinely. Nevertheless, the method did not gain universal popularity at the time because of equivocal results obtained by others, and it remained for the experimental animal studies to reawaken interest in hormonal alteration therapy.

3. *Experimental Research on Animals.*—Much of our present knowledge of the pathogenesis of mammary cancer was obtained from animal studies, particularly on mice. At first the methods were indirect, such as by castration, and then later direct, after the sex hormones were identified, by their experimental use in the production and prevention of the disease.

a. Genetic Factor: Early work on the inbreeding of mice (Little; Slye; Tyzzer) established the role of heredity as a factor in the development of breast cancers in these animals and produced strains with a predictable incidence of the disease that could be used experimentally. It is not certain whether the predetermination is dependent upon the chromosome, cytoplasm, or other cellular elements, but it is established that the incidence of breast tumors in mice can be influenced by genes (Heston; Little). Transplantation pattern experiments with breast carcinoma in mice revealed that each neoplasm had its own pattern that was retained through many passages, suggesting that somatic mutation may be the immediate change that makes some cells cancerous (Furth and others). However, the share of heredity in carcinogenesis may vary in nature and degree in different tumors, strains, and species.

b. Milk Factor: Bittner (1936, 1947) demonstrated an extrachromosomal factor in the milk of lactating female mice of a high-mammary-cancer strain. He could raise the incidence of the tumors in low cancer strains by means of foster nursing upon the high-cancer-strain female. This work was confirmed by others (Andervont; Endocrine-Cancer Conference). Furthermore, this agent has been characterized as similar to a virus and has recently been isolated by Graff and his co-workers (American Association for Cancer Research, 1949). The excellent experimental studies on this milk factor (American Association for Cancer Research, 1949; Andervont; Bittner, 1936, 1947; Twombly, 1940) have definitely established it as an important link in the chain of evidence regarding the genesis of mammary carcinoma in mice.

c. Estrogen: The important role of hormones in the development of breast cancer, as postulated by the early clinical workers, was confirmed in the laboratory.

Lathrop and Loeb, in 1916, demonstrated that ovariectomy in mice could reduce the incidence of spontaneous mammary cancers in high cancer strains, if carried out before the age of 6 months. Further work revealed that ovariectomy between 3 and 5 months of age could prevent mammary cancer almost entirely; between 5 and 7 months of age, the incidence was reduced and cancer appearance was delayed, and after eight months of life, there was no appreciable reduction in incidence (Loeb). Other investigators confirmed these observations (Cori, Murray, 1928). Using crystalline estrone benzoate, Lacassagne (cited by Nathanson, 1944 *a* and *b*) was able to produce mammary carcinoma in high-cancer-strain male mice, in which the disease had not been seen before. It was also found that the appearance of the cancer could be hastened in female mice of high cancer strains, and that the incidence could be raised in females of low cancer strains (Lacassagne, 1936, 1939; Lacassagne, cited by Nathanson, 1944 *a* and *b*) by estrogen injections. These studies were confirmed and extended (Gardner, 1941, 1944; Haagensen and Randall; Suntzeff and others). The breast cancer rate in mice is believed to be higher in breeding than in nonbreeding females (Cori; Lathrop and Loeb; Murray, 1928, 1937; Suntzeff and others), possibly because of the increased amount of circulating estrogen during pregnancy, since the incidence in virgin females can be raised to that in breeding females by estrogen administration (Suntzeff and others). Furthermore, administration of synthetic estrogenic compounds, such as diethylstilbestrol (Shimkin and Grady) and triphenylethylene (Perry and others; Robsen and Bonser), which are of different chemical structure and not related to carcinogenic hydrocarbons, can produce the same results.

In comparing the mammary structures of high- and low-cancer-strain mice, it was found that precancerous nodules of alveolar hyperplasia occurred in 43% of the former and rarely in the latter, irrespective of which of the three primary factors (genetic, milk, estrogen) was lacking (Bittner and others; Gardner, 1944). It was, therefore, concluded that the three factors were etiologically important in precancerous hyperplasia and mammary cancer in mice (American Association for Cancer Research, 1946; Bittner and others). The genetic and hormonal factors may create a suitable substrate for the carcinogenic action of the milk factor (Endocrine-Cancer Conference). The milk factor, however, may not be necessary in rats, which ordinarily have a low incidence of breast cancer, since it was possible to produce mammary carcinoma with metastases by prolonged administration of estrogen (Eisen, 1942; Geschickter; Nelson). However, after halting the estrogen administration or by injecting progesterone, others noted that the tumors regressed and did not consider them to be malignant (Noble and Collip). Therefore, it was suggested, but it is not definite as yet, that estrogens can produce the disease in a species with a nontumorous genetic constitution and without the extrachromosomal milk factor (Nathanson, 1944*a*).

d. Inherited Hormonal Influence: There may be an inherited hormonal influence involved, since transplants of the ovaries from a female of high cancer strain into spayed hybrid mice gave a significantly higher incidence of mammary tumors than transplants of ovaries from low cancer strains (American Association for Cancer Research, 1946; Bittner and Huesby). The high-cancer-strain ovary may give off secretions that are more carcinogenic, on a genetic basis, when all other factors are equal (American Association for Cancer Research, 1946; Bittner and Huesby). Other endocrine glands may also be involved in the hormonal produc-

tion of breast carcinoma in mice, possibly on an inherited hormonal influence basis. Cramer and Horning, in 1936, suggested that the adrenal gland may be concerned in the causation of mammary cancer in mice. Woolley, Fekete, and Little (1939, 1940) and Woolley and Little found that ovariectomy at birth in high-cancer-strain mice did not decrease the high incidence of breast carcinoma as much as expected. These animals showed development of a nodular hyperplasia of the adrenal cortex with subsequent feminization, reversal of castration atrophy of sex organs, and development of mammary glands with carcinoma. These results did not occur in low-cancer-strain mice (Woolley and others, 1940). Adrenalectomy in the spayed animals further decreased the incidence from 33.5 to 9.3% (Shimkin and Wyman). The inference is that estrogens produced by the adrenal gland of high cancer strains can take over the function of the ovaries after their removal early in life. In those animals with this inherited hormonal influence, breast cancer can be produced (Llusia; F. Smith). This is probably mediated, at least in part, through the anterior lobe of the pituitary gland and may function genetically as a mechanism influencing cellular changes in the adrenal cortex after castration (F. Smith). In the high-cancer-strain mice with adrenal cortical hyperplasia, the hypophysis was enlarged and congested but showed no castration cells. Transplants of anterior pituitary glands into high-cancer-strain females increased the incidence of mammary cancer in unspayed animals, but this could not be demonstrated in low-cancer-strain mice (F. Smith). Hypophysectomy in high-cancer-strain mice lowered the incidence of carcinoma, and no definite corpus luteum was seen in the ovaries (Korteweg and Thomas), implying that the lack of gonadotropins prevented the action of the ovaries. These experiments lend support to the concept that a specific inherited hormonal influence may be active in certain strains of mice, allowing for marked susceptibility of the animal to endogenous estrogen produced by the ovaries or the adrenal glands (Heston).

e. Prophylaxis and Treatment in Animals: In order to prevent the appearance of these mammary carcinomas, Lacassagne (1936) suggested the administration of androgens. Testosterone was found significantly to lower the incidence of the breast cancers in mice of high cancer strains (Gardner, 1944; Heiman, 1944, 1945; E. E. Jones; Loesser; Nathanson, 1950; Nathanson and Andervont). Prolonged testosterone administration, beginning shortly after birth, prevented the development of the ovary as well as that of adrenal hyperplasia, with the result that breasts were rudimentary and carcinoma did not arise (Heiman, 1944; Loesser; F. Smith). Delay of androgen administration until later in life caused a progressive increase in the number of cancers obtained, until soon before the expected appearance of the tumor there was no protection by the injections (Loesser). Testosterone when administered with estrogen lowered the incidence and delayed the appearance of breast cancer in mice (Gardner, 1944). The mechanism of action of the androgen may have been through neutralization of the effects of circulating estrogen, inhibition of the production of pituitary gonadotropins, or production of a hormonal imbalance unfavorable to the cancer cells. Attempts to decrease the incidence with the use of desoxycorticosterone or progesterone have not been uniformly successful (Burrows and Hoch-Ligetti), although Heiman (1945) has reported a significant decrease with progesterone administration to a level which was further lowered by use of testosterone. Once the carcinoma was

established, androgen or progesterone therapy or hypophysectomy had no effect on the course of the disease in mice (Gardner, 1944; Heiman, 1945; Nathanson, 1950; Nathanson and Andervont). Nevertheless the success of testosterone in the prophylaxis of mammary tumors in mice and the partial success of castration in human beings have suggested hormonal alteration in women as a prophylactic or therapeutic measure.

4. *Human Studies.*—Further evidence of the relationship of estrogen to human breast cancer was sought, to add to that acquired from the early attempts at castration (Beatson; Boyd; Lett and others; Schinzinger; Thomson), since there are many differences between mouse and human mammary carcinoma (Nathanson, 1950; Panel on Tumors). Furthermore, other species (Gardner, 1944), such as Rhesus monkeys (Pfeiffer and Allen), do not develop carcinoma after estrogen administration.

The fact that 99% of breast tumors occur in women points to a hormonal influence (Panel on Tumors). The peak age incidence of the disease in women is 47 years, and the median age is 52 years, the time corresponding to the hormonal imbalance period produced by the menopause (Nathanson and Welch; Nicolson and Grady). About 5 times as many women with breast carcinoma have a delayed menopause (Olch), and 10 times as many have not had a previous oophorectomy (Herrell) as compared with a similar age group without the disease. Even after castration or the menopause, estrogens can be found in the urine (Frank and others; Nathanson and others; Panel on Tumors; H. C. Taylor, 1944), with their origin possibly from the adrenal cortex (Burrows, 1945; Llusia; Nathanson, 1944*b*). The incidence of breast cancer is higher in nulliparous women (2:1) than in women who have been pregnant, and this suggested that the former may have an endocrine disorder which affects both their reproductive ability and their incidence of breast disease (Chase; Nicolson and Grady). Furthermore, among patients with chronic cystic mastitis due to endocrine imbalance, the incidence of mammary carcinoma was almost five times higher than among normal women (Chase; Logie; S. Warren). There were some investigators who considered fibrocystic disease of the breast, particularly with atypical papillary hyperplasia, as a precancerous condition (Foote and Stewart; Logie; Prudente, 1945; S. Warren), similar to that seen in rodent breasts after administration of estrogen (Eisen, 1942; Gardner, 1944). Pregnancy and lactation, periods when circulating hormones are at a maximum, are known to be associated with an increase in breast carcinoma growth (Chase; A. H. Rosenthal). In women with a previous operation for breast carcinoma, pregnancy within five years of operation may be followed by recurrences of the disease (Trout; S. Warren). Frequently associated abnormalities of the uterus or ovaries occur in conjunction with breast cancer (Hodgson, and others; Nathanson, 1944; Pierce and Slaughter; Speert 1948), and coincidental ovarian, uterine, and breast carcinomas are seen in the same patient more frequently than would be expected by chance occurrence (Hertig and Sommers; Hodgson and others; Speert, 1948; H. C. Taylor, 1931). Thus, the whole reproductive system may be under the influence of an abnormal estrogen stimulus in these patients.

The part played by heredity is not definitely known as yet in human beings (Little). A hereditary history of cancer could be obtained in about 20% of a series (Chase; Nicolson and Grady) and of breast cancer in about 6% (Nicolson

and Grady). Whether a chromosomal or extrachromosomal milk factor could be involved has not been proved (Little), although "cancer families" have been reported in which a milk factor might have been involved (Kennaway and Kennaway; Wood and Darling). There are evidences of a "greater than chance" incidence of certain types of tumors in a given family or in twins, showing that persons of similar biological origin tend to reproduce conditions conducive to the formation of similar types of tumors (Blank; Little). Many stranded (polytene) chromosomes have been demonstrated in two human breast adenocarcinomas, with a greater relative frequency associated with a higher grade of malignancy (Biesele and Poyner). However, these alterations may be a result of the neoplastic change, rather than a cause. In man, there may be an "internal carcinogenic environment" (Cramer), similar to the "inherited hormonal influence" seen in mice (F. Smith). The prophylactic use of testosterone on an intermittent basis might be rational in this type of patient, particularly if fibrocystic disease of the breast, suggestive of hyperestrinism is present (Lacassagne, 1936; Wood and Darling). Heiman (1945) also suggested the use of progesterone to decrease the amount of testosterone needed for prophylaxis. These hormones probably interfere with the early stages of abnormal growth by a direct effect upon the mammary gland or by inhibition of pituitary gonadotropins, and thus indirectly decrease the amount of estrogen produced by the ovary (Heiman, 1945).

5. *Mechanism of Estrogen Action in Breast Carcinogenesis.*—Estrogen is essential for the development and preservation of the mammary gland epithelium, without which there is no tissue upon which a carcinogen can act. Whether the estrogen acts as would a carcinogenic hydrocarbon, to be adsorbed by an acceptor on the cell surface (Bergmann; Berrill), or by a physiologic proliferation to produce neoplastic cells is still hypothetical (Nathanson, 1944*a*).

a. Breast Feeding: In mice, rapid breeding and nonsuckling, involving ovarian stimulation with chemical irritation of the mammary gland due to stagnation, can lower the threshold for breast carcinoma and increase the incidence (Bagg). There is no definite evidence in human beings that faulty lactation can produce more breast cancers (Foote and Stewart), but Nathanson (1944*b*, 1950) believed that this could be a factor. In mice, Lacassagne (1936, 1939) showed that there was a high percentage of estrone in colostrum and in the cystic cancerous breast. By spectrochemical studies with triphenylethylene, it was noted that the precancerous hyperplastic tissue had a great deal of the estrogen substances for prolonged periods, some with altered absorption spectra. Apparently the precancerous tissue had difficulty in eliminating the hormone, and the estrogen may have been changed in structure (Perry and others). Lacassagne (1936) suggested that the estrogen may be transformed by stagnation into a carcinogenic agent similar to other carcinogenic steroids with estrogenic properties. However, another study, with radioactive diethylstilbestrol, showed no selective absorption of the estrogen in the breasts of mice (Twombly and Schoenewaldt).

b. Hyperestrinism: There is strong evidence that the physiologic action of estrogen in producing hyperplasia of the mammary glands may be the factor involved, since synthetic estrogens (Perry and others; Robson and Bonser; Shimkin and Grady) are also active in the process. Furthermore, the development of the cancer can be followed histologically in mice from hyperplastic precancerous

stages to the neoplastic condition (Eisen, 1942). In human beings, the evidences of fibrocystic disease with hyperestrinism of long standing might coincide with stagnation and/or physiologic stimulation (Wood and Darling). However, only 1 of 13 women who died of breast carcinoma revealed pituitary changes of a chromophobe adenoma type that might be considered as evidence of a hyperestrogen effect (Steiner and Dunham). In addition, there appears to be no quantitative difference in the estrogen excretion of high- and low-cancer-strain mice (Karnofsky and others, 1944), or in human beings with breast cancer (Nathanson, 1943; Pearlman; Pincus and Pearlman; Ross and Dorfman; H. C. Taylor and others; Yolton and Rea). These findings, however, do not rule out the possibility that an increased amount of estrogen was present previous to the appearance of the carcinoma, nor do they necessarily give a true index of the rate of secretion, utilization, or destruction of the hormones in the body. Furthermore, the relative sensitivity of the tissue to estrogen cannot be determined (Nathanson, 1944*b*, 1950).

Of interest in regard to destruction of endogenous estrogen are H. S. N. Greene's studies (1941). He noted an increase in uterine and mammary tumors with organ changes indicative of hyperestrinism in rabbits that had damage to the liver due to toxemia of pregnancy (1941). Therefore, attempts were made to determine the capacity of the liver to destroy estrogen in cancerous and noncancerous patients. In a few cases, including breast and ovarian cancer, the tendency of the liver to destroy estrone was absent, but further studies are needed to determine the significance of this finding (Twombly and Taylor). Among patients with breast cancer, those with inoperable cancer had a high percentage of abnormal results on liver-function tests that could not be explained by liver metastases, whereas patients with operable cancer had the same results on liver-function tests as did normal women (Tagnon and Trunnell). However, it is possible that the other factors, such as malnutrition with a vitamin B deficiency, might alter the liver function and estrogen metabolism in these advanced cases. Furthermore, there are several studies which indicate that cirrhosis in human beings does not predispose to breast cancer (Speert, 1949); thus, liver deficiency may not be a factor in man.

Although estrogens have been used to a great extent in medicine, there is no definitive proof that the exogenous hormone can produce cancer in human beings (Geist and Salmon). There have been some reports of development of breast cancer during or after estrogen administration in women, but these cases may have been coincidental (Allaben and Owen; Auchincloss and Haagensen; Foote and Stewart; Parsons and McCall). Cramer has estimated from mice experiments that estrogens would have to be given continuously for many years to produce carcinoma in human beings. Nevertheless, information is still inadequate on the relative sensitivity and rapidity of estrogen action in the mouse and man. Therefore, intermittent, rather than prolonged or continuous, therapy might be safer (Allaben and Owen; Auchincloss and Haagensen).

6. *Hormonal Alteration in Treatment.—a.* Castration: Attempts to decrease the amount of estrogenic stimulation of breast neoplasms by castration were reevaluated in the 1930's, and the problem is still being studied on a therapeutic and prophylactic basis. It is difficult to summarize the reports on irradiation castration, since many times the metastases were also irradiated (Halberstaedter and Hochman). Ahlbom, in 1930, reported equivocal results in 163 patients treated by this method. He could not demonstrate a prolongation of life in his series, but about

one-third had more pronounced improvement than would be expected with local irradiation of the metastases alone. Beneficial effects of castration were confined mostly to premenopausal women. About 15 to 30% of these patients were improved objectively (Adair and others, 1945; DeCourcy; Dresser; McCullagh; Nathanson, 1947, 1950; G. W. Taylor) and 56 to 73% subjectively (Dresser; Halberstaedter and Hochman; Nathanson, 1947, 1950), with an increased sense of well-being, better hematopoiesis, and better appetite. Bone metastases reacted most favorably, with relief of pain and evidence of regression or calcification occurring in 15 to 30% (Adair and others, 1945; Clarkson and Barker; Dresser; Freid and Goldberg; Halberstaedter and Hochman; Leucutia, 1944; Nathanson, 1947; Pohle). In addition, metastases to the lung and pleura (Adair and others, 1945; Archer and Cooper; Freid and Goldberg; Halberstaedter and Hochman; McDonald and Guiss; Nathanson, 1947; Pohle; G. W. Taylor) responded fairly well, with an occasional response of the primary lesion and skin and local recurrences (Adair and others, 1945; Archer and Cooper; Beatson; Halberstaedter and Hochman; Lett and others; McDonald and Guiss; G. W. Taylor; Torek). Rarely was there a response of liver or brain metastases (Adair and others, 1945; Halberstaedter and Hoch-

TABLE 1.—*Hypothetical Pathogenesis of Breast Cancer*

Predisposing Factors	Precancerous State	Precipitating Factors	Breast Cancer
1. Genetic	⟶	1. Somatic mutation	⟶
2. Milk factor		2. Adsorption of carcinogen on cellular surface	
3. Hyperestrinism		3. Hyperstimulation by estrogen	
4. Inherited hormonal influence		4. Milk factor	
5. Chronic cystic mastitis or stagnation			

man; McDonald and Guiss; G. W. Taylor). These effects have prompted several studies to determine the prophylactic value of castration at the time of radical mastectomy (Halberstaedter and Hochman; G. W. Horsley; J. S. Horsley; Snapper), which would also reduce the danger of pregnancy (Trout; Wintz). Although results with surgical castration have been promising in one series (G. W. Horsley; J. S. Horsley), other investigators believed that castration by surgical methods or irradiation should not be used as a routine measure (Ahlbom; Leucutia, 1944; Nathanson, 1947, 1950; Panel on Tumors; Ritvo and Peterson; Snapper).

Improvement was temporary, usually lasting eight months to two years (Halberstaedter and Hochman; Nathanson, 1950), although occasional survivals of five years or more have been reported (Clarkson and Barker; Freid and Goldberg). This has prompted suggestions that estrogen production has recurred from ovaries incompletely destroyed by irradiation (Nathanson, 1950; Nathanson and others, 1940; Panel on Tumors) or from the adrenal glands (Chase; Halberstaedter and Hochman; Panel on Tumors), as noted in mice after gonadectomy (Llusia; Woolley and others, 1939, 1940). Attempts at irradiation of the adrenal glands have not given definitive results as yet (Halberstaedter and Hochman). Therefore, an agent, such as testosterone, that could cause a physiologic castration with decreased adrenal function or neutralization of estrogen at the end-organ might be of real value.

b. Clinical Use of Androgen Therapy: Androgen therapy has been used with some success in cases of breast cancer, in the form of testosterone propionate given intramuscularly (Adair, 1947, 1948, 1949 *a* and *b*; Adair and Herrmann; Adair and others, 1949; Council on Pharmacy and Chemistry, 1947, 1949, 1951; Cutler and Schlemenson; Farrow and Woodard; Fels; Herrmann and Adair; Herrmann and Woodard; H. W. Jones; Karnofsky and others, 1950; Klass; Loesser; McCullagh; McGraw; Mellors and others; Nathanson, 1950; Preston and others; Prudente, 1945; Schwander and Marvin; Segaloff and others, 1951; Stoll; Sylven and Hallberg; S. G. Taylor and others, 1948; Ulrich; Watson and Fetterman) and by subcutaneous pellet implantation (Adair, 1947, 1949*b*; Adair and Herrmann; Loesser; Preston and others; Stoll; Sylvén and Hallberg; S. G. Taylor and others, 1948), methyltestosterone given orally (Boger; Council on Pharmacy and Chemistry, 1951; Cutler and Schlemenson; Preston and others; S. G. Taylor and others, 1948), and testosterone acetate given intramuscularly (Ulrich). Newer products being tested are methylandrostenediol by all three routes of administration (Council on Pharmacy and Chemistry, 1951; Henderson and Weinberg; Homburger and others) and testosterone cyclopentenyl propionate (Council on Pharmacy and Chemistry, 1951).

Loesser and Ulrich in 1939 independently reported on two cases each that appeared to be benefited by androgen therapy. Farrow and Woodard, using small doses of testosterone, reported relief of pain in about half of their 33 cases, but no objective effect with these doses was noted. Fels reported favorable objective as well as subjective response in two of his three patients, using larger doses of testosterone, and Boger gave methyl testosterone orally with regression of osseous metastases in his patient. Adair (1947, 1948, 1949*a* and *b*; Adair and Herrmann; Adair and others, 1949; Herrmann and Woodard) used larger doses of testosterone propionate and confirmed that in certain cases, particularly when bone metastases were present, the hormone was a potent agent capable of producing a striking clinical improvement. Because of the significance of this advance in cancer research, a Subcommittee on Steroids and Cancer was established by the Council on Pharmacy and Chemistry of the American Medical Association, with the object of coordinating the clinical studies on androgens and estrogens among the many investigators (Council on Pharmacy and Chemistry, 1947, 1949, 1951).

(1) Subjective improvement: In several large series of cases, administration of high doses of testosterone propionate resulted in symptomatic relief in 46 to 90% of women with advanced breast carcinoma (Adair, 1949*a* and *b*; Council on Pharmacy and Chemistry, 1949, 1951; Cutler and Schlemenson; Garland and others; Karnofsky and others, 1950; Nathanson, 1950; Prudente, 1950; Sylvén and Hallberg; S. G. Taylor and others, 1948). This was manifested by a dramatic relief of pain from osseous metastases in 75 to 83%, noted within two to four weeks of therapy (Adair, 1949*a* and *b*; Nathanson, 1950; Garland and others; Preston and others; Prudente, 1950; S. G. Taylor and others, 1948), as well as increased appetite, strength, weight, and sense of well-being. Dyspnea, cough, headache, and nausea disappeared in 85% of the patients (Adair, 1949*b*). A bedridden patient was often seen to be relieved of suffering, to be able to sleep without sedation, and to return to work or her household duties after several months of treatment. This is a marked advance in the palliation of the disease (Adair, 1947, 1948, 1949*a* and *b*; Adair and Herrmann; Adair and others, 1949; Chase; Council on Pharmacy

TABLE 2.—*Androgenic Treatment of Advanced Breast Carcinoma*

Author	No. of Cases	Dose of Testosterone Propionate, Mg./Wk., Intramuscularly	Improvement: Subjective	Improvement: Objective: Osseous	Improvement: Objective: Soft Tissue
Ulrich, 1939[c]	2	Testosterone acetate, ?* amount	2	..	2
Loesser	2	1,500-1,850 mg. intramuscularly and by pellet over 3 mo.	2	..	2
Farrow and Woodard	33	5-75 mg./wk. for 10-12 wk	16 (50%)	0	0
Fels	3	75-100	3	1	1
Adair and Herrmann	11 (O†-3, S-8)	300 and by pellets	4	3	1
Boger	1	210 of methyltestosterone	1	1	..
Herrmann and Adair	7-S	400-600	6	..	2
Herrmann and Woodard	14-O	300	13	7	..
Schwander and Marvin	5 (O-3, S-3)	75-100	3	1	0
Cutler and Schlemenson	19 (O-7, S-12)	300 and methyltestosterone, 210	8	1	7
H. W. Jones	15 (O-5, S-10)	300	6	4	2
McGraw	12 (O-8, S-6)	200-300	11	4	2
Mellors and others; American Association for Cancer Research, 1948	59 (O-42, S-77)	300	Greatly exceeded objective improvement	7 (17%)	12 (15%)
S. G. Taylor and others, 1948	24	300-700 and by pellets	46%	35%	..
Adair and others, 1949	70	300	75%	19%	15%
Council on Pharmacy and Chemistry, 1949	285 (O-82, S-77, B-126)	150-300	62%	18%	20%
McCullagh	16	300-600	9 (56%)	?	?
Preston and others	17-O	150-700; pellets in 3 cases	85%	25%	..
Sylvén and Hallberg	38 (O-26, S-12)	300; also methyltestosterone in pellets	88-90%	20-37%	?
Watson and Fetterman	7 (O-3, S-4)	400-500	7	2	3
Karnofsky and others, 1950	56-O, 56-S	300	74%	13 (23%)	14 (21%)
Nathanson, 1950	65	150	53 (83%)	16 (25%)	Occ.
Garland and others	218-O	75, 150, 300, or 600	70%	18%	..
Homburger and others	7	Methylandrostenediol, 25 mg./day in oil, 100 mg./day aqueous or oral, and pellets	7	2	2
Prudente, 1950	60-O, 25-S	175-1,400	80%	20%	31%
Council on Pharmacy and Chemistry, 1951	441	75, 150, 300, or 600	52-58%	10-18%	17-26%
Faloon and others	6	300	3	2	..
Godwin and Escher	15-S	600 for 4 wk	?	..	7
Henderson and Weinberg	28	Methylandrostenediol, 25 mg./day in oil, 100 mg./day aqueous or oral, and pellets	14 (50%)	7 (25%)	?
Segaloff and others, 1951	13-O, 11-S	350	?	5 (38%)	3 (27%)
Stoll	86-S	200 or pellets	?	..	39%

* ? indicates no information given.
† O indicates osseous lesions; S, soft-tissue lesions, and B, both types.

and Chemistry, 1947, 1949, 1951; Ulrich). Patients with soft-tissue lesions usually required two months' treatment or more for symptomatic relief (Council on Pharmacy and Chemistry, 1949; Herrmann and Adair). The exact mechanisms by which testosterone produces these subjective benefits are not completely understood. Certainly, the anabolic protein- and electrolyte-retaining actions of the hormone are involved (Abels and others; Albright; Geist and others; Kenyon and others; Nathanson, 1947; Sylvén and Hallberg), since withdrawal of testosterone therapy leads to a loss of the previous weight gain in many cases (Adair and others, 1949; Herrmann and Woodard; Nathanson, 1950; Schwander and Marvin). Another factor is the stimulating effect of the sex hormones on the bone marrow (Council on Pharmacy and Chemistry, 1949), since refractory anemias of late metastatic breast carcinoma may respond to testosterone therapy with an increase to normal levels after several months. Subjective improvement can be expected to last for one year or more in over 50% of the patients benefited (Council on Pharmacy and Chemistry, 1949).

(2) Objective improvement: (*a*) Bone metastases. Seventeen to 38% of patients with osteolytic metastases, treated with adequate doses of testosterone, showed arrest or recalcification after three to six months of therapy (Adair and others, 1949; Council on Pharmacy and Chemistry, 1949; Garland and others; Karnofsky and others, 1950; McCullagh; McGraw; Mellors and others; Panel on Tumors; Preston and others; Prudente, 1950; Segaloff and others, 1951; Sylvén and Hallberg; S. G. Taylor and others, 1948; Watson and Fetterman). The highest percentage of objective improvement was in skull metastases (Council on Pharmacy and Chemistry, 1951). Bone repair of the metastatic regions may have been involved rather than a specific inhibition of the tumor cells (Sylvén and Hallberg), since pathologic fractures frequently healed, a generalized increase in osseous density was noted, and absorbed rims of bones could be restored to normal contour (Adair, 1948; Karnofsky and others, 1950; Nathanson, 1950; Preston and others; Watson and Fetterman). Furthermore, blood alkaline phosphatase levels often rose, and the serum phosphorus and calcium sometimes decreased, revealing evidence of bone regeneration (Adair, 1947, 1948, 1949*a* and *b*; Adair and Herrmann; Adair and others, 1949; Council on Pharmacy and Chemistry, 1947, 1949, 1951; Sylvén and Hallberg; S. G. Taylor and others, 1948). The metastases were occasionally "snowed under" by osteoblastic deposition of calcium around the carcinoma cells, seen roentgenologically as a dense zone of bone around the local lesion (Adair, 1948; Adair and others, 1949). This concept is supported by experimental studies in which bone regeneration properties of testosterone have been determined (Albright; Gardner and Pfeiffer; Reifenstein and Albright). The marked relief of bone pain observed as a subjective response cannot always be ascribed to arrest or regression of the lesion, since some patients have symptomatic relief while their metastases are believed to be progressing (Council on Pharmacy and Chemistry, 1947, 1949, 1951; DeCourcy; Preston and others; Prudente, 1950; S. G. Taylor and others, 1948). Therefore, an undetermined mechanism may also be involved.

(*b*) Soft-tissue metastases. Testosterone therapy caused objective improvement in 15 to 39% of soft-tissue metastases within two to five months (Adair and others, 1949; Council on Pharmacy and Chemistry, 1949; Godwin and Escher; Karnofsky

and others, 1950; Nathanson, 1950; Prudente, 1950; Segaloff and others, 1951; Stoll). Occasional striking improvement was noted in the primary tumor, carcinomatous ulcer, skin recurrences, lymph nodes, and lung and pleural, hepatic, cerebral, and uterine metastases (Adair and others, 1949; American Association for Cancer Research, 1946, 1948, 1949; Council on Pharmacy and Chemistry, 1949; Cutler and Schlemenson; Fels; Herrmann and Adair; H. W. Jones; Karnofsky and others, 1950; Klass; Loesser; McGraw; Mellors and others; Prudente, 1950; Stoll; Ulrich; Watson and Fetterman), in descending order of frequency. Infrequently a primary inoperable tumor regressed sufficiently for radical surgical measures to be performed (Godwin and Escher; Prudente, 1950). Histological effects, as seen in a few of the responding cases, were pyknosis of the nuclei and hydropic degeneration of the cytoplasm, associated with a marked increase in fibroblastic activity (Adair, 1947, 1948; Adair and others, 1942; American Association for Cancer Research, 1948; Godwin and Escher; Herrmann and Adair; Lowenhaupt and Steinbach; Prudente, 1950; S. G. Taylor and others, 1948). Whether the action of the hormone in these cases was primarily on the tumor cells, the vascular bed, or the stroma is not known (Council on Pharmacy and Chemistry, 1951; Godwin and Escher). Perhaps some of the neoplastic cells were destroyed, with resultant scarring and pressure upon the remaining cancer tissue (Adair and others, 1949; Godwin and Escher). However, these effects are not specific for hormonal therapy, since they may occur with irradiation (Godwin and Escher).

(3) Variability of response: It is not possible to predict the degree or type of response that will be obtained with steroid-hormone therapy in any particular patient. Any combination of improvement, lack of response, or even acceleration of the disease may be seen when the case is studied in respect to the subjective, bone, and soft-tissue results (DeCourcy). The reason for this variability in response has not as yet been determined (Cutler and Schlemenson; Nathanson, 1950; Preston and others), but several factors are known.

(*a*) Hormonal studies. Menopausal status appeared to have no influence on the response to androgens, since the conditions of about equal numbers of premenopausal and postmenopausal women were improved on therapy with testosterone (Adair, 1947, 1948; Adair and others, 1949; Council on Pharmacy and Chemistry, 1951; Nathanson, 1947, 1950; Panel on Tumors; S. G. Taylor and others, 1948). However, among premenopausal women, the best response was obtained in those with a marked suppression of estrogenic activity and signs of masculinization (Klass; Loesser; Preston and others). This evidence supports the view that testosterone acts by means of its physiologic castration effect, as well as its systemic beneficial properties (Nathanson, 1950).

Recent hormonal studies on testosterone-treated patients may aid in clarifying the mechanism of action and the variable response with androgen therapy (Faloon and others; Segaloff and others, 1951). In 45 treated patients there was a decrease in gonadotropin excretion, with a concomitant increase in prolactin and 17-ketosteroid excretion. In those patients whose conditions improved with therapy, there were a decrease in urinary creatine, probably secondary to tissue repair, and a decrease of questionable significance in urinary corticoids (Segaloff and others, 1951). The latter finding is of more significance when combined with results of another study in which those patients whose conditions improved were demon-

strated to have had an inhibition of corticotropin by the testosterone administered (Faloon and others). Opposite findings were noted in those patients who did not respond to therapy (Faloon and others; Segaloff and others, 1951). Furthermore, corticotropin administration has been found to be of no real value in breast cancer and may even accelerate the disease in some cases (Pearson and others, 1949, 1950; Proceedings of First Clinical ACTH Conference; S. G. Taylor, 1950). It is interesting to speculate whether corticotropin may be stimulating production of a harmful adrenal steroid in these patients.

The endocrine environment may be involved in another manner as well. Occasionally, lesions which have reactivated while still receiving maintenance hormonal treatment may have another regression after the discontinuation of therapy or on the administration of the opposite sex hormone (Adair, 1949*b*; Council on Pharmacy and Chemistry, 1949, 1951; Karnofsky and others, 1950; Panel on Tumors). Future studies on hormonal balance in patients treated with steroid hormones and pituitary and adrenal irradiation are strongly indicated.

(*b*) Dosage. Dosage has some effect upon the response, since small doses frequently do not bring about the favorable subjective and objective improvement that is seen with larger doses (Adair, 1949*b*; Adair and Herrmann; Adair and others, 1949; Council on Pharmacy and Chemistry, 1951; Herrmann and Woodard; H. W. Jones; McGraw; Preston and others; Prudente, 1950; S. G. Taylor and others, 1948; Watson and Fetterman). Although 150 to 350 mg. of testosterone propionate per week was believed to be the optimal dose for most patients (Council on Pharmacy and Chemistry, 1947, 1949, 1951), occasional patients required 700 mg. or more each week for prolonged periods in order to obtain the best response (Adair, 1949*b*; Karnofsky and others, 1950; Preston and others; Prudente, 1950; S. G. Taylor and others, 1948). There was suggestive evidence that doses of 150 mg. per week gave the best subjective response (75%) and osseous recalcification (32%), while 600 mg. per week acted best upon the soft-tissue regression (30%) (Council on Pharmacy and Chemistry, 1951). After 10 to 12 weeks of injection therapy, the patient could usually be prescribed a permanent maintenance dose of methyltestosterone, 60 mg. per day (Council on Pharmacy and Chemistry, 1947). A total dose of 3 gm. of testosterone propionate is recommended for maximal subjective and objective improvement (Council on Pharmacy and Chemistry, 1949, 1951; Preston and others), but in a few cases up to 11 gm. has been administered before improvement occurred (Adair, 1949*b*; Adair and others, 1949; Karnofsky and others, 1950). The recommended therapeutic dose of methyltestosterone is 200 mg. per day orally for at least a 30-gm. total. Thus, the minimal duration of this therapy is about twice that for testosterone propionate. In general, these doses gave responses that were similar to those of testosterone given intramuscularly in 17 patients (Council on Pharmacy and Chemistry, 1951). Bone lesions required about three months and soft-tissue lesions about five months to show objective results (Council on Pharmacy and Chemistry, 1951). The recommended therapeutic dose of methylandrostenediol is 100 mg. per day of the aqueous preparation for intramuscular use (Henderson and Weinberg; Homburger and others).

In order to produce the desired effect of inhibiting estrogenic action, particularly in premenopausal patients, doses may need to be somewhat higher (Geist and

others) than in postmenopausal patients, even though the latter do excrete some estrogens (Ellis and others, *b*; Frank and others; Nathanson and others; Panel on Tumors; H. C. Taylor, 1944). Doses of 200 mg. of testosterone propionate per month did not suppress estrogenic function in premenopausal women, whereas a dose of 500 mg. per month did this temporarily (Geist and others). Loesser stated that 700 mg. of testosterone was required for the "hormone atrophy dose," as noted on endometrial biopsy, when hyperestrogenism was present. This further substantiates the better results seen with relatively high dosage in some cases and the need for such dosage in maintenance therapy (Adair, 1949*b*; Preston and others; Prudente, 1950; S. G. Taylor and others, 1948).

(*c*) Grade of malignancy. Malignant tumors of low grades appeared to respond to hormone therapy oftener than the anaplastic ones (Halberstaedter and Hochman; Lowenhaupt and Steinbach; Stoll; S. G. Taylor and others, 1948). Perhaps the slowly proliferating neoplasm can be more effectively buried by fibroblastic and osteoblastic response to testosterone (Lowenhaupt and Steinbach). Another factor may involve the more effective testosterone action on better differentiated cancers which may yet require some stimulation by means of estrogen. Therefore, inhibition of estrogen may allow the natural defenses of the body to produce an arrest or regression (Halberstaedter and Hochman).

(*d*) Type of osseous metastases. The incidence of bone metastases varied with the stage of the disease. Several studies indicated that 50 to 75% of patients with metastatic breast cancer had this complication (Freid and Goldberg; Garland and others). About 95% of these patients had severe, unremitting bone pain (Garland and others), although metabolic studies occasionally demonstrated a spontaneous phase of bone repair (Schilling and others). There was an 85 to 90% incidence of osteolytic metastases (Adair and others, 1949; Freid and Goldberg; Garland and others), with increased calcium and phosphorus excretion (Schilling and others). In patients whose condition improved with androgen or estrogen therapy, there was a decrease in the mineral excretion, with evidence of bone repair. On the other hand, a reverse effect was noted in those patients in whom the hormone accelerated the disease (Schilling and others). The other 10 to 15% of patients with osseous involvement had osteoblastic metastases and exhibited a marked tendency toward calcium and phosphorus retention. The further retention of minerals with steroid-hormone therapy may not be an indication of tissue repair, since this effect could be produced by acceleration of tumor growth. Therefore, the response to therapy is more unpredictable in this type of metastasis. Occasionally, an osteoblastic lesion was seen to decalcify with testosterone therapy (Preston and others).

If it could be proved that the steroid hormones induce deposition of minerals primarily in the areas of the neoplastic tissue, then perhaps hormonal administration with therapeutic doses of radioactive phosphorus would induce a local radiation death of the tumor cells. This study conceivably could extend to include osteoblastic metastases from prostatic carcinoma treated with estrogen and osseous metastases from other types of cancer. Since estrogen, in general, has a stronger effect on mineral retention than androgen, which has mainly a protein anabolic effect (Schilling and others), use of the former may be indicated in such studies.

In summary, there are no specific criteria for determining which case will respond to hormone therapy. H. S. N. Greene's studies (1951) are of interest in this respect. By transplanting the breast carcinoma tissue into the anterior chamber of the eye in male and female guinea pigs, he could determine in which sex the tumor was inhibited. By this method, he believed that one can predict whether androgen or estrogen therapy will be of benefit.

Because of the variable response, roentgen irradiation to localized lesions may add to the palliation in many cases, particularly when highly malignant metastases are involved (Archer and Cooper; Council on Pharmacy and Chemistry, 1947, 1949, 1951; Freid and Goldberg; Garland and others; Kesmodel; Lowenhaupt and Steinbach; McDonald and Guiss). However, when irradiation fails, when the disease is generalized, or when lung metastases are present, hormonal therapy is the logical and sole palliative measure affording some improvement (Council on Pharmacy and Chemistry, 1951; H. W. Jones). Complete or partial objective response may be obtained with testosterone therapy in about 20% of cases for nine months to two years (Council on Pharmacy and Chemistry, 1949).

(4) Prophylactic use of testosterone: The use of testosterone prophylactically after radical mastectomy was suggested as a routine procedure on the basis of animal experimentation (Gardner, 1944; Heiman, 1945; E. E. Jones; Lacassagne, 1936; Lacassagne, cited by Nathanson, 1944*a* and *b*; Lathrop and Loeb; Loesser; Murray, 1928; Nathanson and Andervont). In human beings, irradiation castration has not given striking results in prophylaxis (Ahlbom; Leucutia, 1944; Panel on Tumors; Ritvo and Peterson; Snapper). However, there have been some encouraging reports on surgical castration, whereby the five-year survival rate was raised from 43.5 to 76.9% (G. W. Horsley; J. S. Horsley). Adequate doses of testosterone (Geist and others) not only may produce a functional castration by inhibition of F. S. H. (Auchincloss and Haagensen; Faloon and others; Geist and others; Heiman, 1945; Segaloff and others, 1951; Stoll) but may also prevent hyperplastic adrenal activity following castration by decreasing corticotropin (Faloon and others; Llusia; F. Smith) and may inhibit estrogen at the end-organ (American Association for Cancer Research, 1948; Geist and others; Lacassagne, 1936; Robson; Stoll). In this connection, the vaginal smear may prove useful as a sensitive indicator of androgenic effect whenever testosterone is used in treatment (Geist and others). Testosterone administration, like castration (J. S. Horsley) could prevent pregnancy (Geist and others), which may reactivate carcinoma cells that have not been completely removed by operation (A. H. Rosenthal; Trout; Wintz). Furthermore, it would avoid the unpleasant menopausal symptoms that follow castration (Nathanson and others; G. W. Taylor) by inhibiting the output of pituitary gonadotropin (Geist and others; Heiman, 1945; Salmon; Snapper). Testosterone may also improve breasts with chronic cystic mastitis and thus inhibit the production of this lesion considered by some to be precancerous (Chase; Logie; S. Warren).

Loesser believed that postoperative testosterone therapy had a definite effect in preventing the appearance of recurrences in three cases and advocated pellet implantation of 500 mg. at the time of radical mastectomy, to be repeated when masculinization decreased. Prudente (1945, 1950) used postoperative intramuscular doses of 25 to 70 mg. per week for Grade I malignant growths, up to 300 mg. per week for Grade IV malignant tumors, continued in four-month periods for years.

He was able to increase significantly his 5- and 10-year survivals in 205 testosterone-treated patients compared with a pretestosterone series. Adair (1948) agreed that testosterone therapy may have a real advantage as a postoperative prophylactic measure and implanted 300-mg. testosterone propionate pellets in 500 patients at operation (Adair and others, 1949). Snapper, using surgical or irradiation castration plus testosterone therapy on an intermittent three-month dosage, did not find any protection by this regimen in patients with axillary metastases. However, these patients were given relatively small doses of 75 mg. of testosterone propionate per week, so that few signs of masculinization appeared. In order to obtain optimal results in preventing metastases it may be necessary to change the hormonal balance and produce definite masculinization, as seen in some of Prudente's patients (1945). A special case, requiring massive dosage of testosterone prophylactically, would be cancer of the breast in pregnancy, with its attendant increase in circulating estrogen and rapid growth. Along with pregnancy termination and radical mastectomy, large amounts of testosterone would be needed to alter the endocrine balance toward the male direction (Chase). Further studies are needed to establish the true value of postoperative administration of testosterone in the prevention of recurrences or metastases.

(5) Side-effects: (*a*) Hypercalcemia. Hypercalcemia is one of the most important and dangerous side-reactions encountered in some patients treated with testosterone. The syndrome includes early symptoms of anorexia, headache, and drowsiness, with nausea, vomiting, and prostration occurring when the blood calcium level is 14 mg. per 100 cc. or higher (Council on Pharmacy and Chemistry, 1947, 1949, 1951; Farrow and Woodard; Herrmann and others, 1949; Preston and others; Schilling and others). The hypercalcemia and dehydration ensuing may produce renal calcinosis with lithiasis and can progress to renal impairment and death (Herrmann and others, 1949; Schilling and others). Farrow and Woodard noted that three patients showed marked hypercalcemia on treatment with small and then larger doses of testosterone. In two of them, estrone therapy also produced the toxic symptoms. Others have also observed occasional patients who react with hypercalcemia (Adair and Herrmann; Adair and others, 1949; Council on Pharmacy and Chemistry, 1949; Henderson and Weinberg; Herrmann and others, 1949; H. W. Jones; Preston and others; Schilling and others; Treves and others), but usually the pretreatment blood calcium level is somewhat elevated in these patients (Council on Pharmacy and Chemistry, 1949; Farrow and Woodard; Herrmann and others, 1949). Spontaneous hypercalcemia may be present in 13 to 23% of patients with osteolytic metastases (Adair and Herrmann; American Association for Cancer Research, 1949; Herrmann and others, 1949; Panel on Tumors; Schilling and others). This is particularly frequent in debilitated immobilized patients (Herrmann and others, 1949; Preston and others) and in those having rapid osteolysis with feeble osteoblastic compensatory attempts (Adair and Herrmann). There are three possible responses of the initial hypercalcemia to androgen therapy:

1. Seventy-one per cent of these patients show a significant decrease to normal levels in the first three months of treatment (Adair and others, 1949; Sylvén and Hallberg), with calcium and phosphorus retention and evidence of deposition in the bones (Gardner and Pfeiffer; Herrmann and others, 1949; Kenyon and others; Reifenstein and Albright).

2. Occasionally, a transitory rise in the serum calcium may occur (Adair, 1948; S. G. Taylor and others, 1948). This may indicate a process in the repair of the bone lesions whereby the new bone cells displace the necrotic ones and thus liberate the salts into the blood stream (Adair, 1947, 1948).

3. A few patients with initial hypercalcemia display a steady consistent rise in the serum calcium to reach toxic levels (Council on Pharmacy and Chemistry, 1949; Farrow and Woodard; Herrmann and others). This may develop in 8 to 13% of the patients receiving testosterone and in 2 to 5% given estrogen therapy (Council on Pharmacy and Chemistry, 1951; Farrow and Woodard; Garland and others; Herrmann and others, 1949) and can proceed to renal insufficiency and death (Herrmann and others, 1949; Karnofsky and others, 1950; Nathanson, 1950; Preston and others). Immobilization of debilitated patients, with its attendant bone resorption and hypercalciuria, may produce progressive renal impairment that can be a factor in determining the onset of toxicity. This syndrome is not usually seen in ambulatory patients unless acceleration of the disease is occurring, in which case sex hormone therapy would be immediately halted in these few patients (Council on Pharmacy and Chemistry, 1951). Therefore, hormone therapy should be used cautiously in debilitated patients, particularly when some hypercalcemia or kidney impairment is already present (Herrmann and others, 1949; Panel on Tumors; Preston and others). Certainly all patients receiving this therapy should have renal-function tests, with initial and follow-up serum calcium determinations (Council on Pharmacy and Chemistry, 1949; Herrmann and others, 1949). Hormone treatment should cease if the serum calcium rises to toxic levels and symptoms occur (Preston and others), since renal damage seems to be cumulative in repeated courses of therapy (Herrmann and others, 1949). An adequate fluid intake is helpful in prevention of this syndrome, and intravenous administration of 250 cc. of sodium citrate every four hours will usually allay the symptoms until the blood calcium returns to normal levels (Council on Pharmacy and Chemistry, 1949; Herrmann and others, 1949).

(*b*) Edema and congestive heart failure. Edema and congestive heart failure were occasionally serious complications of sex-hormone therapy, owing to retention of sodium, potassium, chloride, and water (Adair, 1947, 1948, 1949*a* and *b*; Adair and Herrmann; Adair and others, 1949; Council on Pharmacy and Chemistry, 1947, 1949, 1951; Herrmann and Adair; Kenyon and others; Preston and others; S. G. Taylor and others, 1948). Edema, usually not of a serious nature, was seen in 23 to 35% of the patients and was usually localized in the lower extremities (Council on Pharmacy and Chemistry, 1951; Garland and others). However, congestive heart failure occasionally required the cessation of therapy (Adair, 1947; Adair and Herrmann; S. G. Taylor and others, 1948). Serious effects can usually be avoided by sodium restriction and use of diuretics. Tachycardia and tremor were rarely seen (S. G. Taylor and others, 1948).

(*c*) Signs of masculinization. Signs of masculinization in varying degrees occurred in most patients of all ages receiving adequate testosterone therapy (Abel; Adair and Herrmann; Adair and others, 1949; Council on Pharmacy and Chemistry, 1949; Geist and others; Herrmann and Adair; Karnofsky and others, 1950; Loesser; Preston and others; S. G. Taylor and others, 1948; Watson and Fetterman). Deepening of the voice, amenorrhea, and hirsutism were noted in 61 to

74% of the patients (Abel; Adair and others, 1949; Council on Pharmacy and Chemistry, 1951; Garland and others; Geist and others; Karnofsky and others, 1950; Prudente, 1945; Schwander and Marvin). Increased libido or clitoral enlargement occurred in 20 to 40% and occasionally was annoying enough to require sedation and application of a local anesthetic to the clitoris (Adair, 1948; Council on Pharmacy and Chemistry, 1951; Garland and others). In 10 to 30% of the patients, acne or flushes occurred (Adair and others, 1949; Council on Pharmacy and Chemistry, 1951; Garland and others; Watson and Fetterman). In a few patients, atrophy of the remaining breast and endometrium, pruritus, and regression of scalp hair were noted (Adair and others, 1949; Council on Pharmacy and Chemistry, 1951; DeCourcy; Garland and others; Geist and others; Schwander and Marvin). These signs of virilism did not require the cessation of testosterone treatment, since they disappeared in most premenopausal patients (Adair, 1949*b*; Adair and Herrmann; Adair and others, 1949; Council on Pharmacy and Chemistry, 1949; McCullagh; S. G. Taylor and others, 1948). However, hirsutism and amenorrhea were permanent in some cases (Adair, 1948; Geist and others). Adair (1947, 1948) believed that the closer the patient was to the menopause, the longer would be the amenorrhea after therapy; thus, a few never regained their menstrual periods (Adair and others, 1949). Methylandrostenediol administration did not produce these masculinizing effects, but its therapeutic value is still under trial (Council on Pharmacy and Chemistry, 1951; Henderson and Weinberg; Homburger and others).

(*d*) Fractures. Fractures may occur in aged patients with osteoporosis before good osteoblastic production is present, since their relief of pain is often associated with increased activity (S. G. Taylor and others, 1948). Taylor and his associates (1948) have suggested the use of vertebral braces in these patients during the early months of testosterone treatment in order to prevent collapse of vertebrae.

c. Clinical Use of Progesterone Therapy: Progesterone may also inhibit pituitary gonadotropins and corticotropin and can act directly upon the mammary gland to interfere with hyperestrinism without the masculinizing effects of androgen. Animal experiments suggested that progesterone might be of some value on a therapeutic (Heiman, 1945; Noble and Collip) or prophylactic basis (Heiman, 1945). Loesser implanted 2,400 to 2,800 mg. in two patients with far-advanced metastatic breast cancer. Although their menses ceased, the progress of the disease was not altered. A preliminary report (Council on Pharmacy and Chemistry, 1951) on the use of progesterone in 11 patients revealed that 1 patient had a good subjective response and 1 had soft-tissue and bone-lesion regression. The other patients were not benefited. Side-effects of edema, nausea, and pigmentation of the areolae were infrequent. Further studies with progesterone are in progress (Council on Pharmacy and Chemistry, 1951).

d. Clinical Use of Estrogen: After all that has been noted in regard to the action of estrogen in breast carcinogenesis, it seems paradoxical that this hormone should be found useful in treating carcinoma in some cases. However, Haddow in 1938 noted a diphasic action of carcinogenic hydrocarbons, in that they could stimulate or inhibit tumor growth. The similarity in structure of estrogen to the carcinogens stimulated its trial in experimental animals (Badger and others; Eisen, 1941; Gardner, 1941*b*; Salter and others, 1941). Very large doses of estrogen

inhibited the formation of mammary glands and decreased the incidence of breast tumors in mice (Gardner, 1941*b*; Salter and others, 1941). In rats, large doses of estrogen inhibited the growth of transplanted mammary adenocarcinoma (Eisen, 1941). Preliminary treatment with estrogen inhibited the growth of transplanted sarcoma in low-cancer-strain mice, with the result that it behaved as if it were benign (J. W. Howard and others; Salter and others, 1941). Estrogen injections apparently changed the fitness of the animal as a medium for supporting the continued growth of malignant cells (Salter and others, 1941). Synthetic estrogens acted in a similar fashion (Badger and others; J. W. Howard and others; Walpole and Paterson); therefore, this effect may have been a physiologic one. In mice, estrogen in small doses induced epithelial growth, while the relative amount of hyaline fibrous tissue decreased (Loeb and others). However, large doses over a prolonged period produced the opposite effect, and a marked increase in fibrous and hyaline material was noted with atrophy of the ducts and acini (Loeb and others). Therefore, it is conceivable that small doses may stimulate very cellular carcinoma, while large doses may inhibit it by the production of fibrosis. However, this has been partially substantiated in only a few patients, in whom biopsy of the lesion revealed a marked increase in fibrotic proliferation with degenerating tumor cells after large doses of estrogen (American Association for Cancer Research, 1948; Binnie, 1944; Edwards; Godwin and Escher; Haddow and others; Nathanson, 1950; S. G. Taylor and others, 1948). Nevertheless, it has been suggested that the more cellular and differentiated the tumor, the more responsive it is to high dosage (Ellis,*b*; Halberstaedter and Hochman; Lowenhaupt and Steinbach), although S. G. Taylor and his associates (1948) could not find any definite relationship. Conversely, the studies of Loeb and his co-workers showed that large doses of estrogen might stimulate scirrhous carcinoma, owing to the effect on fibrous production, while small physiologic doses might inhibit this type by inducing epithelial growth. These facts may help to explain the apparent discrepancy in reports from those who believe that the more cellular (Haddow and others) or the more scirrhous carcinoma (Stoll) responds best to estrogen therapy.

Nevertheless, it is still not certain whether inhibition occurs by specific estrogenic action on the tumor cells or the fibrous stroma (Godwin and Escher; Loeb and others) or by a decrease in the production of F. S. H. (Badger and others; Karnofsky and others, 1950; Nathanson, 1950). Large doses of estrogen in human females can prevent follicle ripening and corpus-luteum formation (Zondek). The decrease in pituitary gonadotropin may explain why this hormonal castration occurs, why treatment with both androgen and estrogen is effective in some patients (Herrmann and others, 1947) and why synthetic estrogens act in a similar manner (Badger and others; J. W. Howard and others). Furthermore, if there is an inherited hormonal influence, causing an ovary from high cancer strain mice to give off carcinogenic secretions (American Association for Cancer Research, 1946), inhibition of F. S. H. by exogenous estrogen could decrease production of the abnormal hormone. The beneficial effects of castration in premenopausal women (Adair and others, 1945; Freid and Goldberg; Halberstaedter and Hochman; Leucutia, 1944; Nathanson, 1947; Ritvo and Peterson) could be based on the removal of the carcinogenic secretions or of estrogen per se. However, the former concept does not explain the apparent disease acceleration seen in many premenopausal patients with estrogen treatment, as if the exogenous hormone

reinforced the endogenous carcinogen to produce additive effects (Council on Pharmacy and Chemistry, 1947, 1949, 1951; Haddow and others; S. G. Taylor and others, 1948). Furthermore, castrated young women show frequent favorable responses to estrogen administration, indicating that the estrogenic function of the ovary, rather than age, may be important (Council on Pharmacy and Chemistry, 1949; Nathanson, 1950). Nathanson (1950) suggested that higher doses than those used in postmenopausal women might be more effective in premenopausal patients, since more estrogen is needed to inhibit F. S. H. in the latter. Of 12 premenopausal patients treated with massive doses of diethylstilbestrol, 100 to 400 mg. per day, 3 showed definite regression of their disease (Nathanson, 1950; Panel on Tumors). Further investigation of this approach is in progress (Adair, 1949*b*; Nathanson, 1950). The optimum dose has not as yet been determined; future studies may reveal better results with larger doses (Adair, 1949*b*; Council on Pharmacy and Chemistry, 1947, 1949, 1951; Walpole and Paterson). Nevertheless, with the present dosage schedules, estrogen therapy should be administered only to postmenopausal patients, preferably 5 to 10 years or more past the meno-

TABLE 3.—*Estrogenic Compounds: Results of Therapy* *

Hormone	Dose	No. of Cases	Subjective Improvement, %	Objective Improvement, %			
				Primary Tumor Regression	Soft-Tissue Regression	Lung Lesion Regression	Bone Lesion Regression
Ethinyl estradiol	3 mg./day	53	59	45	67	43	10
Diethylstilbestrol	15 mg./day	231	39	42	53	29	14
Premarin®	30 mg./day	35	35	45	44	8	16
Estradiol dipropionate	10 mg./wk.	21	30	50	45	12	†
Dienestrol	15 mg./day	24	46	13	42	17	†
Dimethyl ether of diethylstilbestrol	30 mg./day	35	34	32	47	19	†

* From table 2 and text, Council on Pharmacy and Chemistry, 1951.
† Insufficient cases.

pause (Council on Pharmacy and Chemistry, 1951). This suggestion is made because the most frequent improvement occurred in patients more than 60 years old, and adverse effects have been noted in several premenopausal and early postmenopausal patients (Council on Pharmacy and Chemistry, 1951; Stoll).

Several estrogenic compounds, natural and synthetic, are being studied by different investigators in the United States according to the recommendations of the Council on Pharmacy and Chemistry (1951; Table 3). Other compounds under trial are estradiol benzoate, monomestrol, and tri-para-anisyl-chloroethylene (Council on Pharmacy and Chemistry, 1951). In England, diethylstilbestrol (1 to 20 mg. per day) and triphenylchloroethylene (3 mg. per day) are being studied most extensively (Binnie, 1944; Ellis and others, *a* and *b*; Haddow and others; Stoll; Walpole and Paterson).

In consideration of the results of treatment, synthetic as well as natural estrogens are evaluated, since the estrogenic action of these compounds is believed to be equivalent in the dosage used (Council on Pharmacy and Chemistry, 1947; S. G. Taylor and others, 1948; Walpole and Paterson). From Table 3, ethinyl estradiol appears to be slightly superior to the other estrogens. Since it is the most potent product, perhaps higher dosages of the others may be just as efficacious (Council on Pharmacy and Chemistry, 1951).

Improvement may not be noted for two weeks to five months after the beginning of estrogen therapy; thus, prolonged administration is necessary before a drug can be considered of no value (Adair, 1949*a*; Herrmann and others, 1947; Nathanson, 1947, 1950; S. G. Taylor and others, 1948). Response is often slower than with testosterone therapy (Adair, 1949*b*; Council on Pharmacy and Chemistry, 1951). A total dose of at least 4 gm. of the synthetic estrogens or premarin® (estrogenic substances, conjugated), or at least 200 mg. of the potent estradiol preparations, is necessary before treatment can be considered of no value (Council on Pharmacy and Chemistry, 1951). Therapy should be continued indefinitely if the patient's condition improves (Council on Pharmacy and Chemistry, 1951; Nathanson, 1947, 1950). If the disease appears to be accelerated, the estrogen therapy should be halted immediately (Council on Pharmacy and Chemistry, 1949, 1951; Nathanson, 1950). Occasionally, testosterone can be used with success in patients who relapse with estrogen therapy or who do not respond within a reasonable trial period (Council on Pharmacy and Chemistry, 1951; Karnofsky and others, 1950; S. G. Taylor and others, 1948), just as estrogen treatment may be successful in patients who relapse with androgenic therapy (Adair, 1949*b*; Council on Pharmacy and Chemistry, 1949). Reactivation of lesions may be seen within two months to several years (Adair and others, 1949; Council on Pharmacy and Chemistry, 1949; Haddow and others; Nathanson, 1947, 1950; S. G. Taylor and others, 1948).

(1) Subjective improvement: Forty to 85% of postmenopausal patients experienced some subjective improvement (Adair, 1949*a*; Council on Pharmacy and Chemistry, 1951; Garland and others; Herrmann and others, 1947; Karnofsky and others, 1950; Nathanson, 1947, 1950; S. G. Taylor and others, 1948). Striking relief of bone pain occurred in many patients despite the fact that osseous metastases showed no roentgenologic change. Dyspnea, anorexia, and malaise disappeared in some cases. The physical condition of these patients improved, since they slept without narcotics, had an increased appetite, and gained weight, and optimism and a sense of well-being were obtained (Adair, 1949*a* and *b*; Adair and Herrmann; Adair and others, 1949; Council on Pharmacy and Chemistry, 1949; Karnofsky and others, 1950; Nathanson, 1947; Panel on Tumors; S. G. Taylor and others, 1948). In most cases, the improvement occurred within four to six weeks (Herrmann and others, 1947), with maximum subjective relief after eight weeks of treatment (Council on Pharmacy and Chemistry, 1949), although some patients did not respond for three to five months (Adair, 1949*a*; Karnofsky and others, 1950). The mechanism of production of symptomatic improvement is not definitely known. Estrogens, like androgens, have beneficial systemic, anabolic, and bone-marrow-stimulation effects (Council on Pharmacy and Chemistry, 1947, 1949, 1951; Herrmann and others, 1947; Nathanson, 1950; H. C. Taylor, 1931). In addition, a change in the endocrine environment may act locally on the lesions to aid subjectively as well as objectively (Nathanson, 1950; S. G. Taylor and others, 1948). If one lesion regresses, subjective improvement is usually noted even though other lesions may be progressing (Nathanson, 1944*a*, 1947, 1950; S. G. Taylor and others, 1948; Walpole and Paterson).

(2) Objective improvement: (*a*) Bone metastases. Since estrogens produce a positive calcium balance in most patients (Nathanson, 1950; Schilling and others) and are known to increase cortical bone regeneration in animals (Gardner and Pfeiffer), objective improvement might be expected in osseous metastases. Although previously estrogen treatment had been considered to inhibit bone lesions in only a few cases (Council on Pharmacy and Chemistry, 1949; S. G. Taylor

TABLE 4.—*Estrogenic Treatment of Advanced Breast Carcinoma*

Author	No. of Patients		Improvement					
			Subjective		Objective			
					Bone		Soft Tissue	
	Under 60 Yr.	Over 60 Yr.	Under 60 Yr.	Over 60 Yr.	Under 60 Yr.	Over 60 Yr.	Under 60 Yr.	Over 60 Yr.
Edwards	..	1	..	..	..	..	..	1
Binnie, 1944	1	3	..	..	..	..	4	
Ellis and others, *b*	99	66	..	..	..	Occ.	13 (13%)	27 (40%)
Ellis and others, *a*	69	52	..	..	..	..	16 (None spectacular)	17 (7 spectacular) 30%
Haddow and others	19	21	..	..	..	..	5	11 (50%)
Herrmann and others, 1947	5	12	1	6 (50%)	..	..	0	8 (68%)
American Association for Cancer Research, 1948; Mellors and others	30 postmenopausal		Greater than objective improvement		..	..	10 (33%)	
S. G. Taylor and others, 1948	22 postmenopausal	19	All had feeling of well-being		? inhibition of further growth in several, but no regression		8	16
Adair and others, 1949	..	35	..	..	..	0 in 4 cases	..	8 (23%)
Council on Pharmacy and Chemistry, 1949	144 postmenopausal		60%		Some		50%	
Lowenhaupt and Steinbach	4	13	..	..	0 in 3	0 in 1	0	8 (60%)
Panel on Tumors	35 postmenopausal		56%+		2 of 6		8 (23%)	
Walpole and Paterson	50 postmenopausal		?		1 of 4		Primary, 10/25=43.5% Lung, 2/7=28.6% Lymph node, 5/26=19.4% Nodules, 1/11=9.1%	
Panel on Tumors	63 bone		85% total		80%		51%	
Nathanson, 1950	85 (soft tissue) premenopausal and postmenopausal		57% bone metastases 37% lung metastases		..	..	..	..
Karnofsky and others, 1950	50 (10 yr. postmenopausal or over 60 yr.)		62%		3 of 8		14 in 42 (33%)	
Garland and others	77 bone		38%		18%		..	..
Council on Pharmacy and Chemistry, 1951	339 postmenopausal		40%		16%		38-53%	
Godwin and Escher	18 postmenopausal		..	..	..	..	9 (50%)	
Stoll	86 (mostly over 60)		..	..	4 of 13		44%	59%

and others, 1948), more recent studies have demonstrated objective responses equal to those seen on testosterone therapy (Council on Pharmacy and Chemistry, 1951; Garland and others; Stoll). However, subjective relief in these cases is still more frequent with androgen therapy (Council on Pharmacy and Chemistry, 1951; Garland and others).

Nathanson (1950) believes that more instances of bone regeneration would have been recorded if cases had been followed for longer periods. The repair mechanism involved with estrogens may be different from that involved with androgens, since roentgenologically the lesions heal differently. With estrogens,

moth-eaten areas appear around the periphery of the metastases. These areas have been shown on biopsy to be islands of attempted recalcification, with possible complete sclerosis of the area after eight months (Council on Pharmacy and Chemistry, 1951; Nathanson, 1950). This is in contrast to the increased osseous density noted around the lesions within three to five months of testosterone therapy (Adair and Herrmann; Adair and others, 1949; Council on Pharmacy and Chemistry, 1949; McGraw; Mellors and others; S. G. Taylor and others, 1948; Watson and Fetterman). Nathanson (1950) was able to obtain objective improvement in 30% of 63 patients treated with estrogens in this manner (American Association for Cancer Research, 1948). Others have noted similar improvement in smaller series of patients (Karnofsky and others, 1950; Panel on Tumors; Stoll).

(*b*) Soft-tissue metastases. The most striking effects with estrogen therapy have been noted in the improvement of soft-tissue lesions (American Association for Cancer Research, 1948; Binnie, 1944; Council on Pharmacy and Chemistry, 1947, 1949, 1951; Edwards; Ellis and others, *a*; Herrmann and others, 1947; Mellors and others; Nathanson, 1947; Stoll; S. G. Taylor and others, 1948). Regressions occurred in 23 to 59% of these lesions after three months of therapy (Adair and others, 1949; Council on Pharmacy and Chemistry, 1949, 1951; Godwin and Escher; Karnofsky and others, 1950; Nathanson, 1950; Stoll; S. G. Taylor and others, 1948; Walpole and Paterson). Grossly, within two or three weeks, the responding primary tumor, lymph nodes, and skin lesions began to change from red to purple or brown and became smaller and flatter. Some eventually became encapsulated (Ellis and others, *b*; Haddow and others; Herrmann and others, 1947; Nathanson, 1950). Occasional carcinomatous ulcers healed by epithelization (American Association for Cancer Research, 1948; Binnie, 1944; Haddow and others; Herrmann and others, 1947; Nathanson, 1947, 1950). Microscopically, after estrogen or androgen therapy, in some cases there was an increase in the fibrous stroma, with degenerating tumor cells containing pyknotic nuclei and hydropic cytoplasm (Adair and Herrmann; Adair and others, 1949; American Association for Cancer Research, 1948; Binnie, 1944; Ellis and others, *a*; Godwin and Escher; Haddow and others; Herrmann and others, 1947; Nathanson, 1950). However, such changes are not pathognomonic of a steroid-hormone effect (Godwin and Escher). Nevertheless, Nathanson (1950) has been able to perform radical mastectomies on 21 patients who had extensive inoperable primary breast cancer with lymph node metastases after a marked regression was induced by estrogen therapy. Blood loss was minimal because the area was so fibrotic. Foci of carcinoma cells were seen in every case, but many appeared to be degenerating. Although it is not expected that this procedure will produce a cure, it may prove to be a valuable palliative method in a patient in whom radical surgical treatment would not have been considered previously (Godwin and Escher; Nathanson, 1950). Furthermore, if the lesion is too large for irradiation to be feasible, estrogen therapy may decrease the size and increase the radiosensitivity so that roentgen-ray treatment with reduced dosage can be used. This has been found to be successful in several cases, but care must be taken to avoid radiation necrosis (Binnie, 1944; Nathanson, 1950). After cessation of therapy had allowed a recurrence, some patients demonstrated a repeated regression if estrogen treatment was restarted (S. G. Taylor and others, 1948).

Pulmonary metastases may also respond well, usually after six months of estrogen therapy, as revealed by roentgenologic evidence of regression of the lesion or pleural effusion (Adair and others, 1949; American Association for Cancer Research, 1948; Binnie, 1944; Council on Pharmacy and Chemistry, 1951; Herrmann and others, 1947; Nathanson, 1947, 1950; Panel on Tumors; Stoll; S. G. Taylor and others, 1948). A recent study reported 12 of 25 patients were thus improved (Stoll). Liver and other intraperitoneal metastases responded in only about 9% of the cases (Council on Pharmacy and Chemistry, 1951). About 25% of the patients maintained subjective and objective improvement for nine months or more (Council on Pharmacy and Chemistry, 1949).

(3) Variability of response: Response to estrogens may vary in a somewhat similar manner as response to androgens (DeCourcy). In some cases striking improvements in skin lesions may be associated with progression of bone, lung, or liver metastases (Herrmann and others, 1947; Nathanson, 1950; S. G. Taylor and others, 1948). In a few cases, administration of either hormone may accelerate the disease (Council on Pharmacy and Chemistry, 1947, 1949, 1951; Farrow; Haddow and others; Herrmann and others, 1947; Nathanson, 1950; Schilling and others), requiring cessation of treatment. A minority of patients do not respond to any hormone (Adair and others, 1949; Council on Pharmacy and Chemistry, 1947, 1949, 1951; Nathanson, 1950; S. G. Taylor and others, 1948). The response in relation to hormonal status, dosage and length of treatment, malignancy of the tumor, and type of osseous metastases has already been discussed. A recent study (Nathanson, 1950) revealed that patients with a poor vaginal estrogenic response, regardless of the estrogen dosage, did not respond well clinically. This suggests that the tissues may be relatively insensitive to estrogen or that inhibiting antihormones may be present. Perhaps still higher dosage may overcome these factors.

(4) Side-effects (Table 5): (*a*) Hypercalcemia. Hypercalcemia has been described with estrogen as well as androgen therapy, but it occurs more rarely (Council on Pharmacy and Chemistry, 1951; Farrow; Farrow and Woodard; Garland and others; Herrmann and others, 1949). Edema and congestive heart failure due to sodium and water retention also occur with estrogen treatment (Council on Pharmacy and Chemistry, 1947; Herrmann and others, 1947; S. G. Taylor and others, 1948). These reactions were discussed in the section on testosterone therapy; similar precautions are necessary when estrogens are being used.

(*b*) Gastrointestinal disturbances. Gastrointestinal disturbances occur more frequently in patients receiving estrogen therapy and include anorexia, nausea, vomiting, diarrhea, or abdominal distress (Adair, 1949*b*; Adair and others, 1949; Council on Pharmacy and Chemistry, 1949; Ellis and others, *a* and *b*; Garland and others; Herrmann and others, 1947; Panel on Tumors; Stoll; S. G. Taylor and others, 1948). Urticaria can occur in rare instances (Adair and others, 1949; Council on Pharmacy and Chemistry, 1949). These reactions may be due in part to a sensitivity to the estrogen given, and occasionally a change to a different preparation will cause them to disappear (Council on Pharmacy and Chemistry, 1949).

(*c*) Genitourinary disturbances. Genitourinary disturbances are frequent enough for S. G. Taylor and his co-workers (1948) to recommend a gynecologic

examination at frequent intervals on these patients. Urinary incontinence is occasionally seen (Council on Pharmacy and Chemistry, 1949, 1951; Garland and others; Nathanson, 1950; S. G. Taylor and others, 1948). The most frequent complication is uterine bleeding, due to marked endometrial hyperplasia, or withdrawal bleeding within a week of halting estrogen treatment (Council on Pharmacy and Chemistry, 1951; Garland and others; Herrmann and others, 1947; Panel on Tumors; Walpole and Paterson). Intermittent omission of therapy for a week may prevent or diminish this effect (Adair and others, 1949; Council on Pharmacy and Chemistry, 1949; Nathanson, 1950; S. G. Taylor and others, 1948). Occasionally, fibroids may enlarge, or hematometra may result from the treatment (S. G. Taylor and others, 1948). Endometrial adenocarcinoma has been recorded as following prolonged estrogen administration in a few cases (Fremont-Smith and others; Gusberg; Hertig and Sommers; Vass). Uterine enlargement may also be seen in several patients (Adair and others, 1949).

TABLE 5.—*Side-Effects with Various Estrogens* *

Side-Effect	Estrogen and Incidence in %					
	Ethinyl Estradiol	Diethyl-stilbestrol	Premarin®	Estradiol Di-propionate	Dienestrol	Dimethyl Ether DES
Hypercalcemia	2	3	5	0	0	3
Edema	32	33	35	50	21	17
Nausea	36	33	27	18	21	20
Vomiting	23	19	22	18	21	14
Vaginal bleeding	15	26	27	59	38	31
Incontinence	15	10	11	5	4	6
Pigmentation						
Areola	57	46	40	41	37	60
Axilla	36	21	5	23	13	34

* From Table 6, Council on Pharmacy and Chemistry, 1951.

(*d*) Other effects. Other minor effects of estrogen therapy include the frequent occurrence of marked pigmentation of the areola, axilla, skin folds of the neck, umbilicus, suprapubic regions (Adair and others, 1949; Council on Pharmacy and Chemistry, 1949, 1951; Garland and others; Nathanson, 1950; S. G. Taylor and others, 1948) and enlargement with tenderness of the remaining breast (Adair and others, 1949; Ellis and others, *b*; Herrmann and others, 1947; Nathanson, 1950; S. G. Taylor and others, 1948).

e. Clinical Use of Cortical Steroids: There have been several patients with metastatic carcinoma of the breast treated with corticotropin injections. Corticotropin was being used to stimulate adrenal cortical hormone secretion in the hope of demonstrating some specific cancer-inhibiting action by these steroids (Pearson and others, 1949; Proceedings of First Clinical ACTH Conference; S. G. Taylor and others, 1950). Pearson and associates (1949, 1950) reported on two patients who were not benefited by such therapy (Proceedings of First Clinical ACTH Conference). Taylor and Morris found that one case was accelerated, while another had a short 10-day improvement with lessening of fever and healing of a carcinomatous ulcer, but metastatic nodes continued to increase in size, and at autopsy there was no evidence of tumor regression (Proceedings of First Clinical ACTH Conference). A later report described two more cases that failed to

respond by objective criteria (S. G. Taylor and others, 1950). Barter noted a case of ophthalmoplegia, due to cerebral metastases from a breast carcinoma, that disappeared after corticotropin treatment. In addition, calcium excretion decreased as though calcium were deposited at the site of bone metastases (Proceedings of First Clinical ACTH Conference). It is possible that an occasional regression may occur by means of the stimulation of adrenal sex-hormone output or a decrease in local tissue edema, rather than a specific action of the adrenal corticoids.

On the other hand, cortisone inhibits corticotropin and thus could depress endogenous adrenal activity (Thorn and others). This might be of advantage in those cases in which adrenal estrogen is believed to reactivate a breast carcinoma. A patient who was treated with cortisone demonstrated a decrease in size of the skin nodules (S. G. Taylor and others, 1950). Further evaluation of adrenal cortical hormone action in breast carcinoma is indicated.

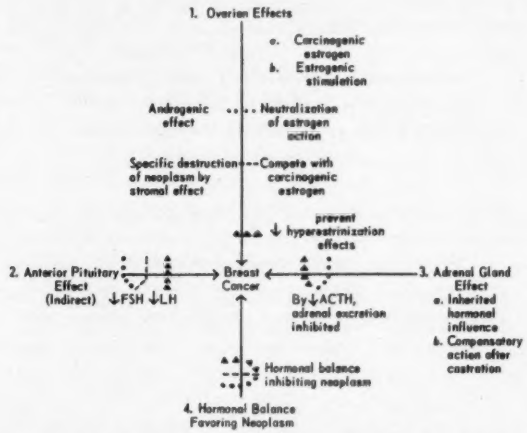


Fig. 3.—Inhibition of predisposing factors. Androgen inhibition factors are indicated by lines of dots; estrogen inhibition factors, by lines of dashes, and progesterone inhibition factors, by lines of triangles.

7. Summary and Conclusions.—The hormonal factors influencing the development of breast cancer can be inhibited by androgen, estrogen, or progesterone administration (Fig. 3). Therefore, the exact site of action of these steroid hormones in treatment is often complicated by a variety of possible mechanisms of action. Nevertheless, definite clinical improvement has been noted after testosterone and estrogen therapy, with the results of all studies summarized in Table 6. Part of the discrepancy in the figures among the authors may be accounted for by consideration of the menopausal status, as demonstrated in the combined studies published by the Therapeutic Trials Committee of the Council on Pharmacy and Chemistry (1951, Table 7).

With the present dosage schedules, testosterone is the hormone of choice in the treatment of premenopausal and early postmenopausal patients. In those patients who are five years or more postmenopausal, estrogen is the choice for treatment of the primary tumor and soft-tissue and lung metastases. In those patients

with symptoms from bone metastases, testosterone therapy produces subjective relief more frequently than does administration of the estrogens. The survival times are definitely increased in patients who respond to hormonal treatment (Council on Pharmacy and Chemistry, 1951), but longer follow-up study is necessary for definitive evaluation. In conclusion, it can be stated that androgen and estrogen therapy has become valuable as a palliative measure in female patients with metastatic carcinoma of the breast.

B. Male Breast Carcinoma

Cancer of the breast accounts for about 0.7% of all malignant growths in males (Sachs) and for about 1% of all breast carcinomas (Huggins, 1949; Nathanson, 1950; Peck; Sachs). Although the incidence of the disease is relatively low, the recent impressive results obtained with hormonal modification warrant close atten-

Table 6.—*Expected Improvement by Steroid Hormone Therapy in Advanced Breast Carcinoma*

Hormone	Type of Patient	Objective			Duration
		Subjective	Bone	Soft Tissue	
Testosterone	Premenopausal and postmenopausal	46-90%	17-37%	15-39%	20% for 9 mo. to 2 yr.
Estrogen	Postmenopausal	40-85%	Occ.-30%	23-59%	25% for 9 mo. or more

Table 7.—*Comparative Improvement with Androgen and Estrogen Therapy* *

Response	Subjective		Primary Tumor		Soft Tissue		Lung		Bone	
Hormone	Testosterone Propionate	Estrogen	Testosterone Propionate	Estrogen	Testosterone Propionate	Estrogen	Testosterone Propionate	Estrogen	Testosterone Propionate	Estrogen
No. of cases	441	339	166	270	316	342	169	139	234	133
Premenopausal patients, %	52	12	22	...	26	24	21	18	10	...
Postmenopausal patients, %	58	40	17	39	23	53	9	38	18	16

* From Chart 1, Council on Pharmacy and Chemistry, 1951.

tion (Chase; Huggins, 1949; McCullagh; Nathanson, 1947, 1950; Treves). Furthermore, the five-year survival rate after radical mastectomy and postoperative irradiation is very low, ranging from 7.5 to 20% (Peck; Sachs). Therefore, the need for an additional treatment method is evident.

1. *Experimental Studies.*—Estrogen administration in high-cancer-strain male mice was followed by the appearance of breast cancers that did not arise without such treatment (Lacassagne, 1939). The milk factor is also essential for the evolution of the disease in male mice, since low-cancer-strain mice, treated with estrogens, had cancers only if they had been nursed on high-cancer-strain mothers (Twombly, 1940). Castrated male mice acquired breast cancers after ovarian transplants (Murray, 1928) or after adrenal cortical tumors had become functional (Woolley and others, 1939). Therefore, the only difference between the incidence of mammary carcinomas in female and that in male mice seems to be the presence of the ovarian secretion in the former.

2. *Human Studies.*—There may be a hormonal factor involved in the evolution of breast cancer in males. The pathologic changes and clinical course of the disease

are similar in both sexes (Huggins, 1949), and it has been suggested previously that an endocrine imbalance could be a factor in the disease in women. The commonest age of the tumor's appearance in men is 57 to 59 years (Peck; Sachs), when hormonal changes in the male climacteric may be active. The endocrine imbalance involved is still not clarified. Estrogen may be considered a possible factor, since it is produced in small amounts by the Sertoli cells of the testis (Huggins and Moulder; Teilum). Opinion varies whether gynecomastia is often seen in association with the cancer (Peck). There was no deviation from the normal low excretion of androgens and estrogens in two male patients with mammary carcinoma as compared with controls of the same age group (Yolton and Rea), but then deviations from normal excretion have not been seen in female patients (Nathanson, 1943; Pincus and Pearlman; Ross and Dorfman; H. C. Taylor and others). Examination of the testes obtained from orchiectomized patients revealed normal or atrophic tubular tissue with slight to moderate hyperplasia of the interstitial cells. No Sertoli-cell hyperplasia was noted (Herrmann; Treves; Treves and others). There have been 13 reported cases incriminating prolonged estrogen therapy of prostatic carcinoma in the production of breast cancer (Abramson and Warshawsky; Campbell and Cummins; R. A. Howard and Grosjean). However, this type of carcinoma is usually bilateral and, therefore, somewhat different from the spontaneous unilateral case. Furthermore, a recent report proved, by acid phosphatase staining, that such breast lesions were metastatic from the prostate, a fact casting some doubt on the previous cases (Campbell and Cummins). Therefore, no definite evidence has been presented that estrogen is a factor in the pathogenesis of breast cancer in male patients.

3. *Treatment.—a.* Castration: The first type of hormonal alteration treatment attempted was testosterone propionate administration in large doses of 925 mg. in 17 days. Metastases were seen to spread rapidly and increase in size (Farrow and Adair; Panel on Tumors). Therefore, castration was performed on the second patient (Farrow and Adair) because of the known temporary benefits of castration in female breast cancer (Beatson; Lett and others; Thomson). The marked improvement of this patient's condition stimulated other trials with this method (Herrmann; Leucutia, 1946; Nathanson, 1950; Treves). The best results were found in patients 60 years of age or older (McCullagh; Treves), results similar to those on estrogenic treatment in women. In the largest series (Treves), 13 patients, striking temporary improvement was noted in 10 patients. Symptomatic benefits included a marked relief of pain within a few days, a gain in weight, strength, and appetite, and a feeling of well-being. Objective improvement included regression of primary lesions, skin recurrences, and lymph node, lung, and, particularly, osseous metastases (Leucutia, 1946; Treves). Similar results were noted by Nathanson (1950) in 10 cases and by Herrmann in 4 of his 6 cases. Treves believed that a definite prolongation of life was effected. When three cases reactivated, he could obtain no further control by estrogen administration or pituitary irradiation (Treves; Treves and others). However, Nathanson (1950) cited two cases in which estrogen therapy produced another regression. There was no noticeable effect upon the metabolic balance of fluid or electrolytes, nitrogen, protein formation, creatine excretion, or carbohydrate utilization, indicating that changes in sex hormone metabolic functions are not necessary for improvement to occur (Treves; Treves and others).

b. Estrogen Administration: There have been a few scattered reports of estrogen trials in therapy of cancer of the male breast (Ellis and others, *a* and *b*; Haddow; Herrmann; Panel on Tumors; Treves and others). If estrogen administration proves to be as successful as castration, it will have the advantages of being less psychologically and physically traumatic as well as more economical. Theoretically, it should produce a functional castration as efficient as orchiectomy. However, only 6 of 15 patients have responded favorably to administration of estrogen alone with similar temporary subjective and objective improvement (Table 8). Possible acceleration of the disease has been noted in a few patients (Ellis and others, *a*; Herrmann; Treves). No definite relationship between response and age could be obtained. Preliminary trials on tumor recurrences after regression induced by orchiectomy have had varying success (Nathanson, 1950; Treves). After a marked regression of an inoperable primary lesion induced with estrogen treatment, Nathanson (1950) was able to perform a radical mastectomy. The patient is living and has been without recurrence for more than four years. Side-effects of toxic hypercalcemia and nausea have been reported (Herrmann; Treves).

TABLE 8.—*Estrogen Treatment of Male Breast Cancer*

Author	No. of Cases	Age, Yr.	Estrogen	Results
Ellis and others, *b*.....	3	1 under 60	Triphenylchloroethylene, 3 gm./day	Improved
		2 over 60	Diethylstilbestrol, 1-10 mg./day	No improvement
Ellis and others, *a*.....	1	?	?	Advanced rapidly
Haddow	1	54	Triphenylchloroethylene, 228 gm.	Pain relieved; nodules regressed; recurrence 6 mo.
Panel on Tumors.....	3	78	Diethylstilbestrol	Good response
		?	.....	Good response; regression of lung and pleural metastases
		?	.....	No response
Treves	3	64, 72	Diethylstilbestrol	No response of postorchiectomy recurrence
		75	Alpha-estradiol (progynon®), 228,000 units in 1 mo.	Increased pain and metastases; hypercalcemia; patient had cirrhosis also
Nathanson (1950)	2	?	Diethylstilbestrol	Regressions after orchiectomy; failure
Herrmann	2 (very short courses)	47	Diethylstilbestrol	Toxic hypercalcemia
		65	Ethinyl estradiol	Nausea; progression of lesions

Further studies are indicated to determine the place of hormonal mechanisms in the pathogenesis and treatment of breast cancer in males. Preliminary investigations have demonstrated that antiandrogenic therapy may be of great aid in the palliation of this disease.

C. Prostate Carcinoma

Biological alteration of the internal environment by castration and estrogen therapy has dramatically influenced the treatment of inoperable carcinoma of the prostate (Gellhorn and Jones).

1. *Need for Endocrine Therapy.—a.* High Incidence: Prostatic carcinoma is found in 15 to 29% of men over 55 years of age (Dean; Deming, 1946; Gutierrez, 1947; Marquardt and Flaherty; McCullagh; Panel on Tumors; Scholl; Young), and there are about 23 cases per 100,000 population (Ackerman and del Regato; Dorn). In 1946, there were 10,616 deaths from this disease (Deming, 1949), and it is listed as the cause of death in 5% of white men over 50 years of age (Huggins,

1947; Okie and others). The incidence is increasing because of the greater life-span, since the neoplasm is most frequent in the aged (Deming, 1946).

b. Late Diagnosis: Diagnosis is made too late for possible cure by radical prostatectomy. About 90% of the cases were inoperable when first seen (Bowler and Pedley; Gutierrez, 1947; Huggins and Johnson; Jewett; Panel on Tumors; Stirling; Strohm; Wear and Schoenenberger; Young), but extension of the criteria for operability and earlier diagnosis resulted in 22.7% of the cases being subjected to radical surgical procedures (Colston). Up to 50% of these patients with operation survived five years or more without recurrences, but the operative mortality ranged from 3 to 11% (Canning and others; Colston; Jewett; Mathe and Ardila; Twinem and Davalos; Wear and Schoenenberger; Young). Early diagnosis is difficult because of the insidiousness of the disease. Symptoms occur late in the course because 75% of the cancers arise in the posterior lobe, requiring extensive infiltration before the urethra and bladder are involved (Bowler and Pedley; Carroll; Cox, 1946; Dean; Huggins and Johnson; Palomo; Twinem and Davalos; Young). In 25 to 42% of the cases metastases have already occurred by the time symptoms arise (Palomo; Wear and Schoenenberger), but there is marked variation in the natural course of the individual case (Colston; Scholl). There is usually an early infiltration of the perineural lymphatics within the gland, by which pelvic lymphatic spread is frequent. Extension continues into the lateral lobes, seminal vesicles, and bladder, but infrequently into the rectum (Colston; Young). Bone metastases, usually by hematogenous spread, are frequent (Palomo; Young) and may cause the presenting symptom of bone pain in a few cases (Huggins and Johnson; Marquardt and Flaherty).

2. *Relationship of Hormones to Prostatic Carcinoma.—a.* Age Incidence: Prostatic carcinoma is a disease of advancing years, with the incidence increasing in direct proportion to age (Huggins and Johnson; Marquardt and Flaherty; Twinem and Divalos). The greatest number of cases are seen in the sixth decade (Huggins and Johnson; McCrae; Palomo), and the average age at recognition varies from 63 to 68 years (Deming, 1946; McCrae; Scholl; Strohm; Wear and Schoenenberger). Therefore, the carcinogenic process may be active for many years before it becomes clinically evident and could be related to an endocrinologic abnormality of the male climacteric.

b. Racial Incidence: Cancer of the prostate is exceedingly rare in Chinese, indicating that a genetic factor may govern the constitutional susceptibility to the disease, possibly through an influence on the endocrine status (R. A. Moore, *a*). A familial history of prostatic carcinoma was obtained in 7% of 429 cases (Strohm).

c. Effect of Sex Hormones on the Prostate: There is no instance of prostatic carcinoma occurring in a eunuch or a true eunuchoid (Dean and others; McCullagh; R. A. Moore, *a*). The prostate of the eunuch remains small, with flat epithelium and acini that are almost devoid of secretion (McCullagh). The fact that castration can affect the secondary sex organs in animals and man has been known for centuries. John Hunter noted that the human prostate underwent progressive atrophy after orchiectomy. Civiale and D'Etoille in the 1830's, and White and Cabot in the 1890's, observed good results in treating nodular prostatic hypertrophy by this method (cited by Dean; Dean and others; Deming, 1946; Herger and Sauer, 1943; Huggins, 1949; R. A. Moore, *a* and *b*). Equivocal results

obtained by others surgeons and better techniques for prostatectomy led this method into discard (Gellhorn and Jones; R. A. Moore, *a* and *b*). Further evidence was needed to establish the relationship of hormone action in the development and physiologic activity of the prostate and prostatic carcinoma.

The discovery of the sex hormones in the 1930's provided additional methods for this study (R. A. Moore, *b*). Androgen therapy was found to cause hypertrophy and hyperplasia of the prostatic epithelium and made secretion possible. Castration and estrogen treatment caused atrophy of the prostatic epithelium and secretion cessation within 7 to 23 days. Testosterone injections reversed these effects in castrates, while simultaneous administration of estrogen nullified the effects of androgen. The crucial balance of these hormones was in a ratio of 1 estrogen : 50 androgen (Barron and Huggins; Huggins, 1943, 1947; Huggins and Stevens; McGraw). Androgen takes part in the regulation of the aerobic oxidation of carbohydrate metabolism in the prostatic tissue, since its absence (castration) or inhibition (estrogen therapy) decreases this phase (Barron and Huggins).

(1) Studies on animals with prostatic tumors: Prostate cancer is a rare disease in animals. It occurs occasionally in dogs but is rarely seen in other species. Administration of estrogens or androgens has not produced this neoplasm (R. A. Moore, *a*), although a typical transplantable adenocarcinoma was obtained in a mouse prostate by a special method of implanting methylcholanthrene (Horning). Since the glandular cells of both the mouse and the human being are dependent upon androgen for maintenance, this method may produce tumors for investigation of the response to hormone therapy. Huggins and his group studied benign tumors of the dog prostate and noted that these masses regressed after castration or estrogen administration and prostatic secretion ceased (Huggins and Clark; Huggins and others, 1939).

(2) Human studies of prostatic carcinoma: Strohm, in 1935, began to use estrogen in the treatment of advanced prostatic carcinoma and produced a marked relief of pain in several cases. At the same time, temporary beneficial results were obtained in a few cases by castration (A. Randall) and testicular irradiation (A. O. Munger, 1941, 1945).

Further studies of androgen control treatment were stimulated by the recognition of a close morphological and physiologic similarity of normal and cancerous prostatic tissue. The neoplastic prostate more frequently preserves its glandular architecture than other cancerous organs (Angrist and Khoury). Kutscher and Wolbergs, in 1935, demonstrated that prostatic tissue is rich in acid phosphatase (cited by Dean; Gellhorn and Jones; Gutman). This enzyme is apparently elaborated by the acinar epithelium and does not appear until puberty; therefore, it seems to be an indicator of physiologic maturity of the prostatic epithelium. Except for occasional highly undifferentiated tumors, prostatic carcinomas contain large amounts of acid phosphatase (Gomori; Gutman; Gutman and Gutman; Gutman and others; Sullivan and others). Dissemination of the cancer outside the prostatic capsule is usually associated with an increase in the serum acid phosphatase from its normal level of 3 to 6 King-Armstrong units (Bowler and Pedley; Gutman; Gutman and Gutman; Herger and Sauer, 1942). There is a large amount of this enzyme near the site of bone metastases (Gutman and others). Thus, Huggins (1944; Huggins and Hodges; Huggins and others, 1941 *b*) postulated that pros-

tatic carcinoma is an overgrowth of adult prostatic epithelium, and, since these cells regress with androgen inactivation or removal, it might be possible to affect the course of the carcinoma by androgen control methods. Accordingly, this theory was tested by castration of patients with advanced prostatic cancer. The procedure produced marked palliation and a decrease in serum acid phosphatase in most cases. In addition, androgen administration produced exacerbation of the disease (Huggins and Hodges; Huggins and others, 1941 *b*; Nesbit and others; Panel on Tumors). Shortly thereafter, estrogen administration was shown to have beneficial effects, similar to those of castration (Herbst, 1942 *a* and *b*, 1943, 1945).

3. *Mechanism of Action in Androgen Control.*—The exact pathogenesis of prostatic carcinoma is not known, but the influence of androgen in activating the neoplasm has been established (Huggins and Hodges; Huggins and others, 1941 *b*; Panel on Tumors). This effect may be mediated through androgen action on prostatic metabolism (Huggins and others, 1941 *b*; Nathanson, 1943). The attempt to decrease this activating influence by castration or estrogen administration has been termed androgen control. Since androgen is produced in the adrenal gland as well as in the testis, consideration of androgen control must also include the effects of such therapy upon the adrenal cortex.

a. Castration Effects (Fig. 4): Castration (1) abolishes testicular androgen immediately and thus (2) decreases the inhibition of the anterior pituitary, so that (*a*) gonadotropins are increased (Kearns), resulting in hot flushes (Nathanson and others), and (*b*) corticotropin is increased, possibly stimulating the release of adrenal androgen (Heckel, 1946, 1948; Kearns).

b. Estrogen Effects (Fig. 4): Estrogen administration (1) inhibits pituitary gonadotropins, so that the production of testicular androgen is decreased in a few days (Heckel, 1946, 1948; C. R. Moore and Price); (2) possibly neutralizes testicular and adrenal androgen before or at the prostatic tissue (Huggins and Clark), and (3) after castration may decrease adrenal androgen activity by preventing the compensatory effects produced by castration (Colston). However, recent evidence indicates that estrogen may stimulate corticotropin production (Tepperman and Tepperman), but it is still uncertain whether adrenal androgen is markedly increased, since urinary excretion studies do not reveal a rise in 17-ketosteroids.

c. Urinary Excretion: Urinary excretion studies revealed that the level of 17-ketosteroids, excretion products of androgens and corticoids, was lower than normal (Fraser and others) in patients with prostatic carcinoma (Frame and Jewett; McHenry and others; Salter and others, 1947; Scott and Vermeulen). However, this decreased level is normal for the advanced age group represented (Frame and Jewett; McHenry and others; Satterthwaite and others; Scott and Vermeulen); therefore increased amounts of urinary androgen cannot explain the onset of the carcinoma. Estriol excretion is also normal for these patients (Crane and Rosenbloom). However, an abnormality in hormone metabolism may be present, since there was a definite tendency for the patients with prostatic carcinoma to convert exogenous estrone into estriol more readily than normal persons (May and Stimmel). This suggests the need for further work on the quantitative fractionation of estrogen and androgen hormones in this disease to reveal whether a general type of abnormality may exist (May and Stimmel; Stimmel and May).

Urinary excretion studies demonstrated the differing physiologic actions of castration and estrogen therapy (Angrist and Khoury; Dean and others; Huggins, 1949; McCullagh; R. A. Moore, *b*; Scott and Vermeulen).

(1) Castration effects: (*a*) Estrogen was decreased, probably because of the removal of Sertoli-cell estrogen.

(*b*) 17-Ketosteroids, after a slight initial fall, rose above pretreatment levels in 45% of the cases (Dean and others). This was explained by compensatory

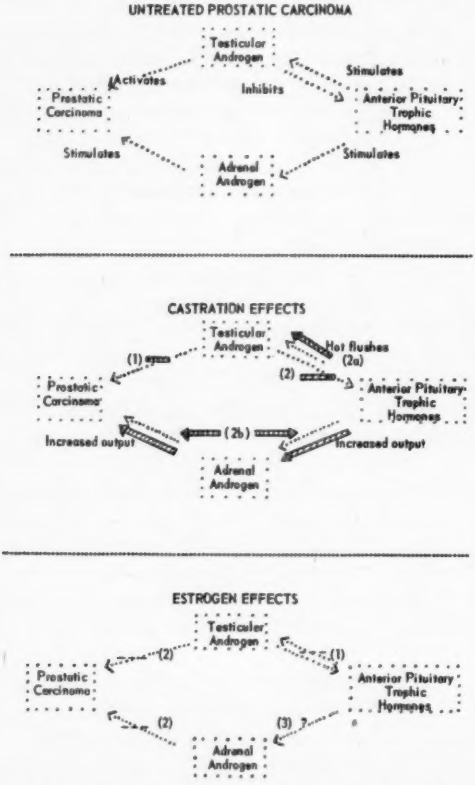


Fig. 4.—Hormonal relationships in prostatic carcinoma. Androgen effects are indicated by arrows of dots; estrogen effects by lines of dashes, and castration effects by large cross hatched arrows. Figures in parentheses refer to items listed under castration effects and estrogen effects in section titled "Mechanism of Action in Androgen Control."

activity of the adrenal gland and may or may not have been due to an increased androgen excretion, since adrenal corticoids were also increased. It is questionable whether the rise or fall in 17-ketosteroids was related to the clinical response (Angrist and Khoury; Dean and others; Satterthwaite and others).

(*c*) F. S. H. was increased, indicating that the testes were still producing a small amount of testosterone that inhibited the pituitary (Deming).

(2) Estrogen effects: (*a*) Estrogen was increased by the addition of the exogenous form.

(*b*) 17-Ketosteroids declined or remained about the same because decreased testicular output may be counterbalanced by an increase in adrenal corticoids.

(*c*) F. S. H. was usually decreased because of the reciprocal action on the gonadotropin output.

Even though the acting physiologic processes are different, the beneficial results of therapy are similar in these methods of androgen control.

4. *Response of the Human Prostate to Estrogen Administration.—a.* Duality of Response: The posterior lobe of the prostate is probably a male structure with a primary response to androgen, whereas the lateral and median lobes (anterior prostate) are ambisexual and respond to male or female sex hormones (Carroll; Huggins and Webster). This is demonstrated in the hermaphrodite, in whom the posterior lobe is present only if the testes are predominant (Carroll). It is significant that there is a predilection of benign tumors for the anterior prostate and of malignant tumors for the posterior lobe. The degenerative effects in the former resemble the cytologic effects induced by estrogenic treatment of prostatic carcinoma, showing that the carcinomatous change may increase the sensitivity of the cells to androgen control (Huggins and Webster). This change could explain why therapy causes greater damage to cancer cells than to normal posterior lobe cells. Failure of response to therapy may be due to the fact that the neoplastic cells retained the resistant properties of the posterior lobe cells.

b. Heterologous Transplant Studies: Heterologous transplants of human prostatic carcinoma into the anterior chamber of the guinea-pig or rabbit eye have provided further biological and chemical evidence of the relationship to androgen-estrogen balance (Deming, 1949; Hovenian and Deming; Krichevsky and Benjamin; Masina). Cancer cells demonstrate autonomy by their ability to metastasize and to be transplanted (Deming, 1949). Early attempts at transplantation were unsuccessful, even with associated testosterone administration, probably because the specimens had not as yet attained autonomy (Masina). Later attempts with metastatic prostatic carcinoma produced successful transplants in male guinea pigs, but not in castrated male or female animals unless they were given massive doses of testosterone (Deming, 1949; Hovenian and Deming). It seems that the biological effect of androgen must be present, but not necessarily in increased amounts, because normal male animals had as much neoplastic growth as testosterone-treated animals (Deming, 1949). Natural and synthetic estrogens produced equal regression of the tumor transplants to approximately 60% of the preinjection size, but these effects were reversible if estrogen administration ceased (Krichevsky and Benjamin). Furthermore, acid phosphatase disappeared from these transplants after castration or estrogen administration (Deming, 1949), demonstrating the chemical as well as the biological effect of androgen control.

After the eighth transplant generation, the tumor became indifferent to the presence of androgen and tolerant to estrogen, with the result that this tumor grew in either sex and was no longer influenced by hormonal methods (Deming, 1949). Acid phosphatase was no longer present in these transplants (Deming, 1949; Hovenian and Deming). Therefore, the cancer had changed chemically as well as biologically. No morphological difference was noted in 16 generations, but longer

studies are necessary, since conversion to an embryonic cell type might explain the biological and chemical independence encountered (Deming, 1949).

5. *Androgen Control in Treatment.*—Castration and estrogen therapy have altered the treatment and prognosis of advanced prostatic carcinoma since their introduction in extensive clinical trials early in the 1940's (Herbst, 1942*a* and *b*, 1943, 1945; Herger and Sauer, 1943; Huggins and Scott; Huggins and others, 1941*b*; A. D. Munger, 1945; Scott and Benjamin; Wear and Schoenenberger). Marked subjective and objective improvement with a prolongation of useful life was often noted for varying periods, but cures were extremely rare unless radical prostatectomy could be performed (Dean; Gellhorn and Jones; Gutierrez, 1947; Herbst, 1942*a*, 1943, 1945, 1947; Karnofsky and others, 1950; Scholl).

The results obtained by estrogen therapy or castration were similar, with only minor differences reported (Karnofsky and others, 1950; Marquardt and Flaherty; Nesbit and others); for this reason various authors preferred the one or the other alone or both in combination (Cox, 1947; Deming, 1946; Herger and Sauer, 1945, 1947; Meads; Veit and Frazier). The immediate subjective and objective effects were very satisfactory in 75 to 95% of the cases (Alyea; Bumpus and others; Chute and Willetts; Crane and Rosenbloom; Deming, 1946; Dodds and others; Herbst, 1947; Herger and Sauer, 1947; Huggins, 1947; Joint Discussion on Cancer; Karnofsky and others, 1950; Kearns; Mathe and Ardila; R. A. Moore, *b*; Nesbit and others; Okie and others; Scott and Benjamin; Veit and Frazier; Wear and Schoenenberger). Various natural and synthetic estrogens have been tested with equal success (Berger and Buu-Hoi; Duncan; Haddow and others; Herbst, 1945; Huggins, 1944; Joint Discussion on Cancer; Kearns; McCrae; Okie and others), although several authors prefer the modified natural hormone, such as ethinyl estradiol, and estradiol benzoate or dipropionate (Dean; Duncan; Herbst, 1942*a*, 1943, 1945, 1947; Kearns; McCrae; Okie and others). The fact that castration and treatment with estrogens of differing chemical structure can produce similar results implies that the physiologic action of testosterone deprivation is involved (Joint Discussion on Cancer) rather than a specific anticancer property of estrogen (Berger and Buu-Hoi; Kahle and others, 1942). The endocrine alteration may change the enzyme systems of the cancer cells with respect to the metabolism of the phosphatase catalysts and thus decrease the size and function of the neoplasm (Huggins, 1943).

a. Subjective Improvement: Marked subjective relief was usually noted within 2 to 4 days after castration and after 7 to 10 days of estrogen therapy. Symptoms of urinary frequency, dysuria, pain, retention, and hematuria were relieved partially or completely, often within 10 days of therapy. This improvement may have resulted from the decrease in prostate size noted most frequently with estrogen treatment (Chute and Willetts; Deming, 1946; Duncan; Fergusson, 1946, 1948; Joint Discussion on Cancer; Karnofsky and others, 1950; Okie and others). In 42 to 86% of the patients, urinary obstruction was temporarily relieved (Alyea; Chute and Willetts; Deming, 1946; Emmett and Hamm; Herbst, 1942*a*; Herger and Sauer, 1945, 1947; Kearns; Nathanson, 1944*a*; Stirling), but if obstruction persisted surgical intervention was indicated as a further measure (Chute and Willetts; Crane and Rosebloom; Deming, 1946; Fergusson, 1948; Joint Discussion on Cancer; Nesbit and Plumb). However, there was usually less need for repeated transurethral resections when estrogen was administered (McCrae). Pain completely disappeared in 50 to 56% of the patients within one to three days after castration

and in 7 to 10 days of estrogen administration (Alyea; Cox, 1947; Dean and others; Deming, 1946; Duncan; Emmett and Greene; Emmett and Hamm; Fergusson, 1948; Herbst, 1942*a*, 1945; Karnofsky and others, 1950; Kearns; R. A. Moore, *b*; Nesbit and Cummings; Nesbit and others; Okie and others; Palomo). Partial relief was obtained in another 22 to 26% of the cases (Chute and Willetts; Colston; Emmett and Hamm; Herger and Sauer, 1945, 1947; Kearns; Nesbit and others). Refractory anemia due to metastatic foci in the bone marrow (Alyea and Rundles) responded in two to five months, with a return toward a normal blood count (Fergusson, 1948; Heckel, 1946, 1948; Herger and Sauer, 1945, 1947; Huggins, 1947; Huggins and others, 1941 *b*; Kearns; R. A. Moore, *b*). Furthermore, 80% of the patients experienced an increase in appetite, weight, strength, and sense of well-being, with a resultant beneficial psychic effect (Bumpus and others; Chute and Willetts; Dean and others; Deming, 1946; Duncan; Fergusson, 1948; Huggins, 1943; Kearns; Marquardt and Flaherty; Nesbit and others; Palomo; Scott and Benjamin). About 50% of the subjectively improved patients maintained their gains for over a year (Fergusson, 1946, 1948; Heckel, 1946, 1948), and many were sufficiently relieved to be able to return to active community life (Chute and Willetts; Cox, 1947; Crane and Rosenbloom; Dean; Dean and others; Deming, 1946; Duncan; Huggins and Scott; Kahle and others, 1942; McCrae; Okie and others).

b. Objective Improvement: (1) Tumor regression: Regression of the local and metastatic lesion is usually seen after several weeks of androgen control. Estrogen therapy produced a softening and shrinkage of the primary neoplasm in 33 to 75% of the cases within three to five months, but regression of bone metastases was noted only occasionally (Chute and Willetts; Dean; Dean and others; Deming, 1946; Fergusson, 1946, 1948; Heckel, 1946, 1948; Herger and Sauer, 1945, 1947; McCrae; McCullagh; Nesbit and others; Okie and others). Perhaps the bone regeneration effects of estrogen (Gardner and Pfeiffer) have not been stressed because of the osteoblastic type of metastases, since hyperossification has been reported around regressed carcinoma cells (Wattenberg, 1947). Furthermore, larger doses of estrogen with a longer period of observation may reveal that these doses are more effective in healing osseous metastases than the smaller amounts in use today (Berger and Buu-Hoi; Gutierrez, 1949; Herger and Sauer, 1945, 1947), as has been suggested in the section on breast cancer (Nathanson, 1950). Soft-tissue metastases in the lung, the mediastinal, inguinal, and supraclavicular lymph nodes, and the superficial nodules shrank or disappeared within two or three weeks (Alyea; Bumpus and others; Dean; Dean and others; Deming, 1946; Duncan; Fergusson, 1946, 1948; Gilbert and Margolis; Herger and Sauer, 1945, 1947; Huggins and Johnson; Kahle and others, 1942; Karnofsky and others, 1950). Convincing evidence for regression of metastases to the spinal cord was demonstrated by several reported cases of relief from cerebrospinal block, with a return of normal muscular power and sensation (Alyea; Clarke and Viets; Cox, 1947; Fergusson, 1948; Huggins, 1946; Huggins and Johnson; Nesbit and Cummings). Bilateral ureteral obstruction with resultant uremia has also been relieved by androgen control therapy (Alyea; Gellhorn and Jones).

Histological alterations have been noted in biopsy specimens and at postmortem examination of estrogen-treated patients with prostatic carcinoma. The acid phosphatase content of the tissue was decreased, and the cytoplasm revealed hydropic degeneration. The nucleus was condensed and pyknotic, with a resultant decrease

in mitotic formation. The cell membranes sometimes ruptured, and nuclei could then be seen to lie free in the acinar space. After several months, most of the malignant tissue was replaced by scar tissue, but neoplastic foci never completely disappeared (Alyea; Deming, 1946; Fergusson, 1946, 1948; Gilbert and Margolis; Haddow and others; Heckel and Kretschmer; Kahle and others, 1942, 1943; R. A. Moore, *b*; Schenken and others; Wattenberg, 1946, 1947; Wattenberg and Rose).

(2) Phosphatase changes: In the 65 to 88% of the metastatic cases with an elevated acid phosphatase level (Alyea; Dean; Dean and others; Fergusson, 1946, 1948; Gutman; Herger and Sauer, 1945, 1947; Nesbit and Baum, 1951; Sullivan and others), a decrease to 60% of the original level was seen within one or two days after castration or within seven days of estrogen therapy (Chute and Willetts; Dean; Deming, 1946; Gutman; Herger and Sauer, 1943, 1945, 1947; R. A. Moore, *b*; Nesbit and Plumb; Okie and others). There was no decrease if the acid phosphatase was normal before treatment (Dean; Dean and others). These changes demonstrated the effects of androgen control on the physiology of the neoplastic cells, and thus the results of therapy could be followed by the chemical values, since they often paralleled the clinical response (Cox, 1947; Dean; Deming, 1946; Gutman; Joint Discussion on Cancer; Parlow).

On the other hand, alkaline phosphatase was above normal in up to 86% of metastatic cases (Emmett and Greene; Nesbit and Baum, 1951) because of the osteoblastic type of bone metastases (Bowler and Pedley; Dean). The postcastration level rose after a few days in 65 to 80% of the cases, and then steadily declined in several months. With estrogen therapy, there was a delayed rise in alkaline phosphatase in 25 to 33% of the cases (Dean; Dean and others; Huggins and Hodges). In some, these changes may have indicated bone healing, but in others the metastatic foci may have been growing larger or new metastases may have occurred, with the result that the alkaline phosphatase level did not parallel the clinical result (Dean; Dean and others).

(3) Prolongation of life (Table 9): Androgen control therapy prolongs the active useful life of the patient with advanced prostatic carcinoma (Emmett and Greene; Fergusson, 1946; Gahagan and Fischman; Gellhorn and Jones; Heckel, 1948; Herger and Sauer, 1947; Karnofsky and others, 1950; Meads; Nesbit and Baum, 1950; Nesbit and Plumb; Palomo; Stirling; Veit and Frazier). This fact has been demonstrated by large series of cases, since the individual course of a single patient may be of long duration (Haines and Miceli; Herger and Sauer, 1947; Nesbit and Baum, 1950; Stirling). In untreated patients, the average duration of life from the first symptom was 31 months. When metastases were present, 66.6% died within nine months, while 58% of patients without metastases at the time of diagnosis died within one year (Bumpus). When transurethral resection and sulfonamide therapy were used, the duration of life was increased (data for "control" in Table 9) over that in the untreated series (Bumpus; Nesbit and Baum, 1950). The further addition of androgen control therapy greatly improved the results obtained in several closed series of cases (Canning and others; Colston; Emmett and Greene; Herbst, 1947; Nesbit and Plumb; Nesbit and Baum, 1950; Palomo; Wear and Schoenenberger; Table 9), since there was a consistently greater percentage of patients living for each of the six-month periods. Furthermore, those patients who died of their disease had a greater survival time when they were treated by androgen control (Table 9). There is definite evidence that

a combination of estrogen therapy and castration is more effective than either alone (Crane and Rosenblum; Nesbit and Baum, 1950; Wear and Schoenenberger), since 36% survived five years after the combination therapy, compared with 26% for orchiectomy alone, 18% for estrogen therapy alone, and 9% in the control series (Nesbit and Baum, 1950). Further prolongation of life might not be effected, since many of these patients are in the elderly age group and they may die of the degenerative diseases rather than of their carcinoma (Bumpus and others; Nesbit and Baum, 1950; Veit and Frazier). Therefore, the treated patients were given a better opportunity to live their normal life span without suffering from their prostatic disease.

c. Variability of Response and "Delayed Failures": About 10 to 30% of patients did not respond to either castration or estrogen therapy (Deming, 1946; Endocrine-Cancer Conference; Herger and Sauer, 1947; Huggins, 1943; Huggins and Johnson; Huggins and others, 1941*b*; Nesbit and Baum, 1950). The condi-

TABLE 9.—*Prolongation of Life with Androgen Control*

Author	Control				Androgen Control Therapy								
	Thompson	Veit and Frazier	Nesbit and Plumb		Nesbit and Cummings	Alyea	Emmett and Grede	Huggins, 1946	Nesbit and Plumb	Veit and Frazier	Herger and Sauer, 1947	Nesbit and Baum, 1950	
			With Metastases	Without Metastases								With Metastases	Without Metastases
No. of cases...	887	74	231	273	75	37	133	20	125	74	130	35	78
Mo. After Therapy		% Alive							% Alive				
0- 6.....	..	80	69	72	93	95	88	..	92-98	95	84	99.0	93.6
6-12.....	75	62	47	64	..	84	78	80	81-94	86	76	91.5	84.7
12-18.....	..	43	31	39	..	..	..	62	71-80	81	60	80.0	80.8
18-24.....	50	38	20	32	66	68	60	45	63-76	72	51	54.3	74.4
24-30.....	..	34	14	25	..	..	56	..	57	63	40	54.3	71.8
30-36.....	30	31	11	22	..	65	..	35	46	58	33	48.6	65.4
36-42.....	..	31	..	..	..	..	..	..	39	57	27	42.9	57.8
42-48.....	..	27	9	14	41	..	..	..	33	..	26	40.0	53.9
48-54.....	..	24	..	..	..	..	..	..	.....	..	26	31.5	53.9
54-60.....	14	23	6	10	..	..	..	25	.....	..	..	20.0	43.6

tion of a few patients may improve subjectively (Dean; Herger and Sauer, 1945, 1947) because of the beneficial systemic effects of estrogen, without objective response. Rarely, a case may appear to be accelerated by estrogen treatment (Haines and Miceli; Herbst, 1942*a*; Nesbit and others). At present, there is no conclusive method of predicting which patients will be benefited by androgen control. Histological examination of the testes from castrated patients revealed no definite abnormality that could be correlated with the response to treatment of the prostatic neoplasm (Angrist and Khoury; Bumpus and others). The testes were usually within normal limits, with moderate tubular atrophy and slight interstitial-cell hyperplasia (Dean; Dean and others; Huggins and others, 1941*b*). Huggins (1942) believed that the unresponsive tumors were of the anaplastic, undifferentiated type without the adult characteristics of endocrine sensitivity found in the well-differentiated adenocarcinoma. Other investigators agreed with this concept (Dean; Endocrine-Cancer Conference; Fergusson, 1946; Parlow; Stirling; Sullivan and others). Some of these tumors did not have an elevated acid phosphatase level when they metastasized, indicating at least a chemical change toward complete autonomy (Deming, 1946), but even among these there were some that responded

to therapy. In a few patients, larger doses of estrogen (Deming, 1949; Fergusson, 1948; Nesbit and others; Twinem and Davalos) or use of a different estrogen preparation (Berger and Buu-Hoi) produced a favorable response. Scirrhous carcinoma usually regressed poorly, owing to the paucity of glandular elements, in comparison with an adenocarcinoma (Fergusson, 1948; Gutierrez, 1949; Huggins, 1944).

The disease recurred with one year of treatment in 30 to 50% of the patients (Emmett and Greene; Huggins, 1943, 1944). A greater incidence of recurrences was seen in direct proportion to the time elapsed, and in time all patients might have recurrences (Carroll; Deming, 1946; Herger and Sauer, 1945, 1947; Karnofsky and others, 1950; Kreschmer; A. Randall). These cases have been termed "delayed failures" (Nesbit and Cummings). Even though the prostate remained small, the metastases were seen to progress rapidly to death (Alyea; Fergusson, 1946, 1948; Gilbert and Margolis; Huggins, 1947). However, the marked pain and suffering noted in patients who had not been treated with androgen control methods were usually not seen (Herbst, 1945; C. R. Moore; Stirling). Higher doses of estrogen or use of a different estrogen preparation (Berger and Buu-Hoi; Cox, 1947) produced a second remission in a few cases. Re-treatment by castration after a "delayed failure" with estrogen therapy has been found to give symptomatic relief in up to 36%, while the reverse procedure has produced symptomatic relief in 29% of the patients (Nesbit and Baum, 1950). In addition, there was an average increase in survival of 9.6 months in those patients who responded a second time (Nesbit and Baum, 1950).

Several explanations have been offered for the mechanism of "delayed failures":

1. Heterologous transplantation experiments demonstrated that after a number of generations the tumor lost its ability for acid phosphatase production and became refractory to androgen or estrogen (Deming, 1949). This is supported clinically by the observation that some of the "delayed failures" did not have a second rise in acid phosphatase after the remission (Deming, 1946, 1949; Fergusson, 1948; Herger and Sauer, 1945, 1947; Nesbit and others). It is possible that the autonomous metastases were better able to effect a change to an embryonic type of cell that was physiologically different but not necessarily morphologically altered (Deming, 1949). This would explain the observation of progressive metastatic growth without growth of the primary cancer (Alyea; Cox, 1947; Fergusson, 1946, 1948; Gilbert and Margolis; Huggins, 1942, 1946).

2. A second theory claims that extragonadal foci of androgen, such as from the adrenal gland, might be providing the necessary androgen for tumor stimulation by compensatory action after castration (Alyea; Huggins, 1943, 1944). This concept is supported by the delayed increase in 17-ketosteroid excretion after castration and the postmortem observation that the adrenal glands were four to seven times the normal size in several cases of "delayed failure" (Deming, 1946; Herbst, 1942*a*). Bilateral adrenalectomy may prove to be of practical value (Cox, 1946; Dean; Huggins and others, 1941*a*) in the future, since a few patients have had temporary amelioration of recurrent symptoms with adrenal or pituitary irradiation (Alyea; Gahagan and Fischman; Harrison and Poutasse; Herbst, 1947; Herger and Sauer, 1947; Panel on Tumors). This may mean that adrenal androgen is involved in stimulating the recurrences in those few patients in whom the cancer is still sensitive to hormone balance (Angrist and Khoury; Deming, 1949). Since there are many patients whose cancer is no longer responsive to hormone therapy,

it is not surprising that a corticotropin-treated patient did not reveal any acceleration or inhibition of his disease (Pearson and others, 1949, 1950). Estrogen prevents the compensatory hypertrophy of the adrenal gland after castration, but "delayed failures" are seen as frequently as with castration (Deming, 1946).

Progesterone inhibits corticotropin production and, therefore, might be useful in this regard. In addition, progesterone is known to inhibit L. H. production; therefore physiologic castration (Trunnell and others), similar to that seen with estrogen administration, might be of benefit as another method for androgen control. There have been two reports of striking clinical remissions and prostate regression in six patients with "delayed failure" who were treated with progesterone (Gutierrez, 1949; Panel on Tumors). A recent study (Trunnell and others) described improvement in about 60% of 19 patients who were treated with progesterone or anhydrohydroxyprogesterone. These patients included some that were previously untreated, as well as several with "delayed failure." In those who improved, the phosphatase levels responded as with other hormonal therapy. In a few patients an apparent acceleration of the disease was noted. The intramuscular administration of progesterone in doses of 50 to 100 mg. per day frequently gave painful reactions and, therefore, was not tolerated for prolonged periods. Pellet implantations are being evaluated in two patients. The recommended dose of anhydrohydroxyprogesterone is 25 to 50 mg. per day by mouth. However, this product gave a higher percentage of tumor acceleration than the progesterone given intramuscularly. The authors concluded that progesterone may be efficacious in some cases, particularly when relapse has occurred after estrogen therapy and castration, but it is not recommended in preference to the other treatment (Trunnell and others).

Finally, cortisone administration may be another method of approach in decreasing adrenal androgen (Harrison and Poutasse), since it is known to cause atrophy of the zona fasciculata and the zona reticularis (Sprague). The latter zone has been incriminated as the possible source of adrenal sex steroids (Burrows, 1945; Tepperman and Tepperman). No clinical trials have been reported as yet with this hormone.

3. A third theory draws from experience with the hormone treatment of breast cancer, in which the opposite sex hormone may produce beneficial results after the cancer has become refractory to the original hormone (Adair, 1949*b*; Panel on Tumors). Therefore, altering the estrogenic environment of the newer cancer cells which have developed in an estrogen substrate by the administration of androgen may effect a temporary remission (H. V. Munger). On the other hand, intermittent administration of estrogen and progesterone may prevent the tolerance that the cancer cells build up to the single hormone environment, without the danger of an androgenic stimulation effect.

d. Time at Which Treatment Starts: From animal experiments, it was recognized that prostatic carcinoma can become refractory to estrogen therapy after eight transplant generations (Deming, 1949). In human beings androgen independence and the presence of metastases affected the survival time adversely (Nesbit and Baum, 1950). Therefore, most authors advocated early orchiectomy and estrogen treatment (Deming, 1949; Dodds and others; Fergusson, 1948; Harrison and Poutasse; Heckel, 1946, 1948; Kearns; Nesbit and Baum, 1950; Rose). However, others have been impressed by the more striking effects produced in patients who

have advanced metastatic disease, and they recommended withholding treatment until symptoms appear (Bumpus and others; Emmett and Greene; Meads; Nesbit and Cummings; Stirling). Some authors advocated estrogen treatment in the early case with supplemental castration when symptoms appear (Herger and Sauer, 1945, 1947; Mathe and Ardila), particularly from osseous metastases (Alyea; Huggins, 1947). Other factors involved in the selection of the best time for beginning therapy included the attempts at prevention of metastases and hormone treatment in conjunction with radical operation.

(1) Prevention of metastases: Some patients do not have evidences of metastases when they present themselves for treatment. Furthermore, in 80 to 90% of such patients the acid phosphatase level is normal (Fergusson, 1946, 1948; Herger and Sauer, 1941, 1942; Nesbit and Baum, 1951; Sullivan and others). It would be desirable to prevent metastases by prophylactic therapy. Heterologous transplantation studies demonstrated the influence of androgen and estrogen upon metastases and the development of complete autonomy after sufficient transplant generations (Deming, 1949). Clinical studies of castration or estrogen therapy started as soon as the diagnosis was established produced conflicting reports of their value in preventing metastases. Some authors believed that there was a lower incidence of metastases in the patients who were treated before such spread was evident (Alyea; Cox, 1946, but others have not noted a prophylactic effect (Deming, 1946; Fergusson, 1948; Herger and Sauer, 1947; Nesbit and others; Stirling).

(2) Preoperative and postoperative treatment with estrogen: Androgen control therapy is palliative for varying periods, and cures are not expected unless radical surgical removal is performed, since foci of neoplastic cells remain in the cancerous prostate. Estrogen therapy is believed to produce the earliest signs of destruction in the periphery of the carcinoma. Therefore, such therapy was suggested as a means of causing regression of the moderately advanced disease that had extended into the apex of the prostate and seminal vesicles so that surgical removal could be performed (Colston; Harrison and Poutasse; Parlow; Young). Even in cases that were operable, routine administration of estrogen was suggested because of the frequent finding of tumor cells in the perineural lymphatics (Colston and Brendler; Young). A clinical regimen of administration of diethylstilbestrol, 1 to 5 mg. per day, for several months is being tested, with radical perineal prostatectomy at the time of maximum regression. By this method, it is hoped that about 80% of the cases can be considered operable and a greater number of patients can be cured of the disease (Colston and Brendler; Gutierrez, 1947, 1949; Harrison and Poutasse; Parlow and Scott; Twinem and Davalos). Perhaps progesterone may also be useful in this regard (Gutierrez, 1949). The presence of metastases is not always a contraindication to radical surgical treatment, since metastatic foci, having responded to hormone treatment, may undergo further regression after the primary lesion is removed (Gutierrez, 1949; Parlow and Scott). After operation, the patient is usually given small maintenance doses of estrogen with or without orchiectomy, to minimize potential metastatic activity (Colston and Brendler; Fergusson, 1948; Gutierrez, 1949; Harrison and Poutasse; Twinem and Davalos). This combined treatment may further increase the life expectancy of these patients and is worthy of further trial (Parlow and Scott).

e. Estrogen Dosage: (1) Therapeutic dosage: The optimum dose of estrogen is not definitely determined as yet and may vary with the type of estrogen used and the sensitivity of the individual cancer. Modified estradiol is approximately six times more potent than the synthetic estrogens; the recommended therapeutic dose is usually 0.10 to 0.15 mg. per day (Karnofsky and others, 1950; Kearns; McCrae). Synthetic estrogens have approximately equal potency, although the neoplasm in some cases may be more sensitive to one than to another (Berger and Buu-Hoi; Walpole and Paterson). Various authors recommended low doses of 1 to 5 mg. per day (Gutierrez, 1947; Haines and Miceli; Herbst, 1942*a*, 1943, 1945, 1947; Nesbit and Baum, 1950), intermediate doses of 10 to 20 mg. per day (Berger and Buu-Hoi; Deming, 1946; Fergusson, 1948), or massive doses of 30 to 300 mg. per day (Cox, 1946; Twinem and Davalos; Wattenberg, 1946, 1947; Wattenberg and Rose) as being more efficacious. Since in some cases the estrogen requirement for producing androgen control is greater than in others, the response of the individual patient to the dosage schedule must be evaluated. Natural estrogens can be used in proportionately greater amounts (Duncan) if the increased dose proves to be of greater benefit. If adverse side-effects cause difficulties, they can often be ameliorated by a decrease in the daily dose (Herger and Sauer, 1947). However, intermediate and large doses are usually well tolerated (Berger and Buu-Hoi; Cox, 1946; Fergusson, 1948). Okie and co-workers recommended the use of two 25-mg. ethinyl estradiol pellets subcutaneously every four months for a constant high estrogen level with minimal inconvenience or side-effects.

(2) Maintenance dosage: Estrogen administration must be continuous throughout the remaining life span of the patient, since reactivation of the neoplasm occurs if the hormone therapy is discontinued for a prolonged period (Berger and Buu-Hoi; Chute and Willetts; Dean; Fergusson, 1948; Heckel, 1946, 1948; Herger and Sauer, 1947; Huggins, 1947). Occasionally, another course of estrogen therapy can control a recurrence in cases of neoplasms that are still responsive to hormone treatment (Berger and Buu-Hoi; Fergusson, 1948; Huggins, 1947). Small doses of estradiol, 0.05 mg. per day (Karnofsky and others, 1950; Kearns; McCrae; Twinem and Davalos), or of synthetic estrogen, 1 mg. per day (Chute and Willetts; Dean; Deming, 1946; Fergusson, 1948; Heckel, 1946, 1948; Herger and Sauer, 1947; Joint Discussion on Cancer), are usually adequate for maintenance, although larger amounts were used by some British investigators (Berger and Buu-Hoi; Cox, 1947; Duncan; Joint Discussion on Cancer).

f. Side-Effects of Estrogen Therapy in Males: (1) Genitourinary effects: In 25%, the penis and testes atrophied, with a decrease in libido and potency occurring in almost all the patients (Chute and Willetts; Dean; Deming, 1946; Fergusson, 1948; Heckel, 1946, 1948; Huggins and Scott; R. A. Moore, *b*; Wattenberg and Rose). However, most patients preferred these estrogen effects to castration, with its surgical expense, psychic trauma of emasculation, and hot flashes (Fergusson, 1948; Huggins and Johnson). Estrogens in small doses controlled the hot flushes after castration (Huggins, 1943; Huggins and Johnson; Huggins and others, 1941*b*. Squamous metaplasia of the urethra and verumontanum was a frequent asymptomatic change during estrogen administration (G. F. Moore and others; Wattenberg, 1946; Wattenberg and Rose).

(2) Effects on breast: Generalized swelling with tenderness of the breasts and areolae was noted in more than 80% of the cases (Alyea; Chute and Willetts;

TABLE 10.—*Estrogen Treatment of Prostatic Carcinoma*

Author	No. of Cases	Drug and Dose	Results
Chute and Willetts	35	Diethylstilbestrol or diethylstilbestrol dipropionate, 10 mg./day	Almost all benefited
Haines and Micell	6	Estradiol dipropionate, 1 mg./day	Four responded well
Heckel and Kretschmer	1	Diethylstilbestrol, 3-12 mg./day	Regression of primary lesion with relief of symptoms and histological changes
Haddow and others	1	Trichlorophenylethylene	
Herbst, 1942 *a* and *b*, 1943, 1945, 1947	20	Estradiol benzoate; diethylstilbestrol; estradiol dipropionate; ethinyl estradiol	Favorable response in 95%
Kearns	78	Diethylstilbestrol, 3 mg./day	60-70% definitely benefited; sedimentation rate helpful in following course of therapy
Herbst, 1942 *a* (Discussion)		Ethinyl estradiol, 0.15 mg./day	
Colston (Discussion)		Estradiol benzoate, 50 mg. pellets	
Kahle and others, 1942	7	Diethylstilbestrol, ? dose	All responded well
Marquardt and Flaherty	10	Diethylstilbestrol, ? dose	50% showed symptomatic and objective improvement
Duncan	3	Estradiol benzoate, 1-2 mg./day, or diethylstilbestrol, 5 mg./day	Improvement in all
Herger and Sauer, 1943, 1945, 1947	130	Diethylstilbestrol, 1-3 mg./day	75% were improved
Dean; Dean and others	29	Diethylstilbestrol, 1-5 mg./day	Symptomatic and objective improvement; acid phosphatase decreased in 84%
Nesbit and others	50	Diethylstilbestrol, 1-10 mg./day	Favorable response in 80%; higher dose often succeeds when a lower dose fails or after postcastration recrudescence
Dodds and others	50	Diethylstilbestrol, ? dose	Favorable response in 90%
Stirling	18	Diethylstilbestrol, 1-5 mg./day	72% symptomatic relief and prolongation of life; surgery and castration in conjunction gave best results
Cox, 1946	30	Diethylstilbestrol or dienestrol, 30 mg./day	Higher dose better
Fergusson, 1946, 1948	30	Diethylstilbestrol, hexestrol, or dienestrol, 2-15 mg./day	84% were improved; histological changes; better results in "delayed failures" with higher doses (60-80 mg./day)
Heckel, 1946, 1948	24	Diethylstilbestrol, 3-25 mg./day	50-60% were improved
Joint Discussion on Cancer	?	Diethylstilbestrol, 1-10 mg./day	Favorable response in 90%
McCrae	15	Ethinyl estradiol, 0.05 mg./day	Improvement in all
Nesbit and Plumb	50	Estrogen, ? dose	Prolongation of life, greater than with castration
Berger and Buu-Hoi	20	Alpha-brom-alpha-beta-beta-triphenylethylene, 15-20 mg./day	Continuous administration needed; benefits in some cases of diethylstilbestrol failure
Colston and Brendler	200	Diethylstilbestrol, 1-2 mg./day	Regression of primary lesion in 75% allowing radical surgical treatment
Gutierrez, 1947, 1949	?	Diethylstilbestrol, 1.5-11 mg./day and 300 mg./day	Tumor regression and symptomatic relief preoperatively, to make 80% operable; benefits in "delayed failure"
Gahagan and Fischman	72	Diethylstilbestrol, ? dose	Prolongation of life in most patients
Parlow and Scott	14	Diethylstilbestrol, 1-5 mg./day	Regression of primary tumor, so that radical surgery feasible; castration used in conjunction
Twinem and Davalos	42	Ethinyl estradiol, 0.1 mg./day	Routine use postprostatectomy
Sheppard (Discussion)	?	Diethylstilbestrol, 300 mg./day	Higher doses gave better results
Karnofsky and others, 1950	?	Diethylstilbestrol, 1-5 mg./day; ethinyl estradiol, 0.1-0.5 mg./day	Objective and symptomatic relief in 50-75%; prolongation of life
Nesbit and Baum, 1950	1,818	Diethylstilbestrol, 1-5 mg./day, or equivalent dose of another estrogen	Definite prolongation of life in 3- and 5-year follow-up observations; best results with estrogen and orchiectomy combined
Harrison and Poutasse	100	Ethinyl estradiol, 0.05 mg./day; diethylstilbestrol, 1 mg./day	Symptomatic and objective improvement in 70%; preoperative tumor regression with estrogen therapy; early orchiectomy and estrogen therapy advised with radical surgical treatment
Okie and others	9	Ethinyl estradiol pellets, 50 mg./4 mo.	Good response in 7; pellet implants recommended for maximal effect and convenience

Dean; Dean and others; Deming, 1946; Duncan; McCrae; McCullagh; Wattenberg, 1946, 1947; Wattenberg and Rose). Histologically, the ducts became elongated, and budding was frequent (G. F. Moore and others; Wattenberg, 1946, 1947; Wattenberg and Rose). There may be less breast stimulation when natural estrogens are used (Joint Discussion on Cancer; McCrae). Bilateral mammary carcinoma in males reported after treatment with estrogens for prostatic carcinoma over prolonged periods (Abramson and Warshawsky; R. A. Howard and Grosjean) may actually have been metastases from the prostatic lesion (Campbell and Cummins). Nevertheless, careful palpation of the breast should be performed before and during treatment.

(3) Edema: There was retention of sodium, chloride, and water, resulting in occasional edema of the lower extremities (Chute and Willetts; Cox, 1946; Deming, 1946; Haines and Miceli; Huggins and others, 1941*a*; McCrae; McCullagh; Wattenberg, 1947; Wattenberg and Rose). If necessary, diuretics and salt restriction can be utilized to prevent this complication.

(4) Miscellaneous effects: Pigmentation of the areolae, midline of the scrotum, and lower abdomen was commonly noted during estrogen therapy (Chute and Willetts; Deming, 1946; Dodds and others; Heckel, 1946, 1948; Joint Discussion on Cancer). Vertigo was occasionally an annoying side-effect (Fergusson, 1946, 1948). In addition, there occasionally was a change to a more feminine complexion, with fat deposition in the suprapubic area (Dean; Dean and others; Deming, 1946; Fergusson, 1948; Herbst, 1947). Rarely, a toxic hepatitis or a skin rash resulted from treatment with synthetic estrogens (Deming, 1946; Fergusson, 1946; Herbst, 1942*b*; Stirling; Wattenberg, 1946, 1947). Gastrointestinal upsets (Dean and others; Deming, 1946; Heckel, 1946, 1948; R. A. Moore, *b*) were produced less commonly with natural than with synthetic estrogens, since the natural form is more likely to be metabolized by the body with fewer reactions (Kearns; McCrae). Occasionally, a change to a different estrogen product decreased these side-effects (Berger and Buu-Hoi; Cox, 1947; Joint Discussion on Cancer).

6. *Summary and Conclusions.*—Estrogen therapy of advanced malignant prostatic growths has produced marked palliation, of a temporary nature, in a majority of the patients treated. The best responses have been noted in the relief of symptoms and in the regression of the primary neoplasm and the soft-tissue metastases. Osseous lesions heal less frequently, but further study of this aspect is indicated. A definite prolongation of life has been produced in many of these cancer patients. Furthermore, preoperative use of estrogen may increase the number of patients who can be given the opportunity for cure by radical surgical removal. Progesterone therapy may also prove of value in the future. The benefits of steroid-hormone administration far outweigh the minor side-effects produced.

The success of androgen control in the treatment of prostatic carcinoma has provided a great impetus for the investigation of cancer chemotherapy, particularly in the realm of internal environmental alteration.

(To Be Concluded)

News and Comment

ANNOUNCEMENTS

International Congress of Dietetics.—The First International Congress of Dietetics will be held from July 7 through 11, 1952, in the Royal Tropical Institute, Amsterdam, Netherlands. Persons who are interested are requested to apply for further details to Miss Diane J. Ten Haaf, General Secretary, Executive Committee, 13 Pomonaplein, The Hague, Netherlands.

International Congresses on Chest Diseases.—The XII Congress of the International Union Against Tuberculosis and the II International Congress on Diseases of the Chest, sponsored by the Council on International Affairs, American College of Chest Physicians, will be held in Rio de Janeiro, Brazil, Aug. 24 to 30, 1952. Both Congresses will be held under the presidency of Prof. Manoel de Abreau; Dr. Reginaldo Fernandes will serve as General Secretary. The Honorable Getulio Vargas, President of Brazil, has accepted the Honorary Chairmanship of the Congresses.

Physicians wishing to present papers at the Rio Congresses on the subject of tuberculosis are requested to write to Prof. Etienne Bernard, Secretary General, International Union Against Tuberculosis, 47 Rue de Courcelles, Paris, France, and those wishing to present papers on non-tuberculous diseases of the chest (heart and lung) should communicate with Dr. Andrew L. Banyai, Chairman, Council on International Affairs, American College of Chest Physicians, 112 E. Chestnut St., Chicago 11.

For further information please write Mr. Murray Kornfeld, Executive Secretary, American College of Chest Physicians, 112 E. Chestnut St., Chicago 11.

GENERAL NEWS

The Art Section of the Army Medical Library.—"The Picture Collection" of the Army Medical Library has grown in size, organization, and use to such an extent that it has become a full-fledged Art Section. In 1948 there were approximately 15,000 items in the collection; now there are well over 21,000 pictures and nearly 13,000 negatives. Acquisitions during the past year included numerous gifts, such as the fine collection of medical bookplates from Dr. Morris Fishbein and a large collection from Dr. Webb E. Haymaker of portraits of neurologists attending the 1949 International Neurological Congress in Paris. The continuing program of exchange with the Armed Forces Institute of Pathology brought in many pictures of medical institutions, and the Library received a collection of portraits from the duplicates in the New York Academy of Medicine. In addition to these large gifts, pictures are acquired through letters of solicitation. In recent months nearly 800 pictures of military and civilian hospitals and more than 500 portraits of Fellows of the American College of Physicians and of Initiates of the American College of Surgeons have been acquired through this means. The Art Section's collection of portraits of Honorary Consultants to the Army Medical Library was also thus substantially augmented in 1951, though it is not as yet complete.

The greatest number of calls for pictures are for portraits of physicians of the past and present and of military medical officers and nurses. Next in frequency are requests for historical material, for hospital pictures, especially hospitals in Civil War times, and for medical subjects. The steady increase in service to the public seems proof of the value of the Art Section.

The Library is always grateful to receive additional pictorial material of medical interest. Gift pictures, or information on pictures available for purchase, should be addressed to the Catalog Division, Army Medical Library, Seventh Street and Independence Avenue, S.W. Washington 25, D. C.

Books

Low-Sodium Diet: A Manual for the Patient. By Thurman B. Rice, M.D. Price, $2.75. Pp. 103, with 14 food charts. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1951.

The factual material provided in this book is reliable, and the physician can safely recommend it to his patients. Those who are above the average in intelligence will be greatly helped by it. The writing is distinct and clear, and the accompanying tables are well arranged. On the other hand, the subject matter seems to the reviewer to be pitched above the heads of many patients, but for them the physician with the help of this book can simplify the instructions it provides.

Patients adhering to these low-sodium regimens are encouraged by the author to keep in touch with their physicians, but less emphasis than is desirable is placed on the hazards which attend such rigid restriction of sodium. Physicians resorting to these diets ought to acquaint themselves thoroughly with the sodium-depletion syndrome.

The author, himself put on a low-sodium diet and, therefore, writing from personal experience, is Professor of Public Health at the Indiana University School of Medicine. Although he is not an authority on circulatory or other diseases in which such diets are prescribed, he has obtained advice from colleagues who are entitled to be regarded as authorities, and assistance from the Dietetics Department of the Indiana University Hospital and the Indianapolis General Hospital.

The foreword to the book is written by James O. Ritchy, M.D., Professor of Medicine, Indiana University School of Medicine.

Handbook of Nutrition: A Symposium Prepared Under the Auspices of the Council on Foods and Nutrition of the American Medical Association. Second edition. Price, $4.50. Pp. 717, with tables and charts. The Blakiston Company, 1012 Walnut St., Philadelphia 5, 1951.

The fact that nutrition is a rapidly developing branch of science can be determined easily by a comparison of the first and second editions of this worth-while handbook. A wealth of new information has accumulated in the eight years since the first edition appeared. The many new developments in the vitamins, in amino acid and protein metabolism, and in therapeutic nutrition, and especially the valuable lessons from World War II, have made it most appropriate that the Council on Foods and Nutrition of the American Medical Association should sponsor this revision. The book, like its predecessor, is a comprehensive and authoritative review by a distinguished group of scientists of the facts on which the science of nutrition is based. Part I is devoted to the basic biochemistry and physiology of the essential components of food. Part II outlines the nutritional needs of man in health and disease, while Part III describes the nutritional deficiency states. Part IV covers the adequacy of the American diet, with considerable discussion of ways in which our diet might be improved. The chapter on foods for emergency use is especially timely. This reviewer can offer but few criticisms. A few of the sections are already out of date, a fault common to most textbooks. Its 717 pages certainly remove it from the category of a handbook. None of the chapters deals specifically with obesity, which is one of our most important nutrition problems today. Nevertheless, this is a *must* book. Everyone interested in nutrition will want a copy in his personal library.

From Dugout to Hilltop. By Margaret Ross Evans Stewart, M.D. Price, $3.75. Pp. 233. Murray & Gee, Inc., 3630 Eastham Drive, Culver City, Calif., 1951.

When a doctor has had a long and varied experience, it is valuable and interesting to have a record of it.

Of the author of this autobiography all the "American Medical Directory" of 1950 has to say is this, and in small type, too:

Stewart, Margaret R. Evans (H) b '74; Calif. 5, '00, Pa. 7, '00; 1 '00; retired

In this book she describes how this brief summary came into being: her early days, her medical school training, her adventures in practice extending over more than forty years, and, finally, her work with the Veterans' Bureau.

It is a pleasant volume, humorous, sad, brave, and very human. It is worth reading.

First Report on Institutional Research Grants of the American Cancer Society. Pp. 258. American Cancer Society, Inc., 47 Beaver St., New York 4, 1951.

The American Cancer Society uses 25% of its publicly contributed funds to support its research program. It has tried to achieve a balanced program by three types of research support:

1. Fellowships to young scientists for specified training in cancer research at designated institutions of higher learning.

2. Grants-in-aid to institutions for the research of individual scientists working on specified, well-formulated projects in any phase of cancer research: basic, applied, laboratory, or clinical.

3. Institutional research grants to institutions of established reputation which conduct integrated programs of cancer research.

This report concerns only the institutional research grants, which are the most recent of the Society's research projects. The institutional research grant is designed as a direct and essentially a program grant, in contrast to the project grants. It provides the responsible director of the research program with both fluid funds and venture capital which may attract other funds into his program.

The first part of the report is an over-all survey of this type of grant and is of great interest. The last part is devoted to the reports of the institutions which have received such grants. The American Cancer Society is to be congratulated on the wisdom which it has demonstrated in the administration of its research funds.

Fifth Annual Report to American Cancer Society, Inc., July 1949-June 1950. By Committee on Growth of the National Research Council. Pp. 384. Division of Medical Sciences, National Research Council, 2101 Constitution Ave., Washington 25, D. C., 1951.

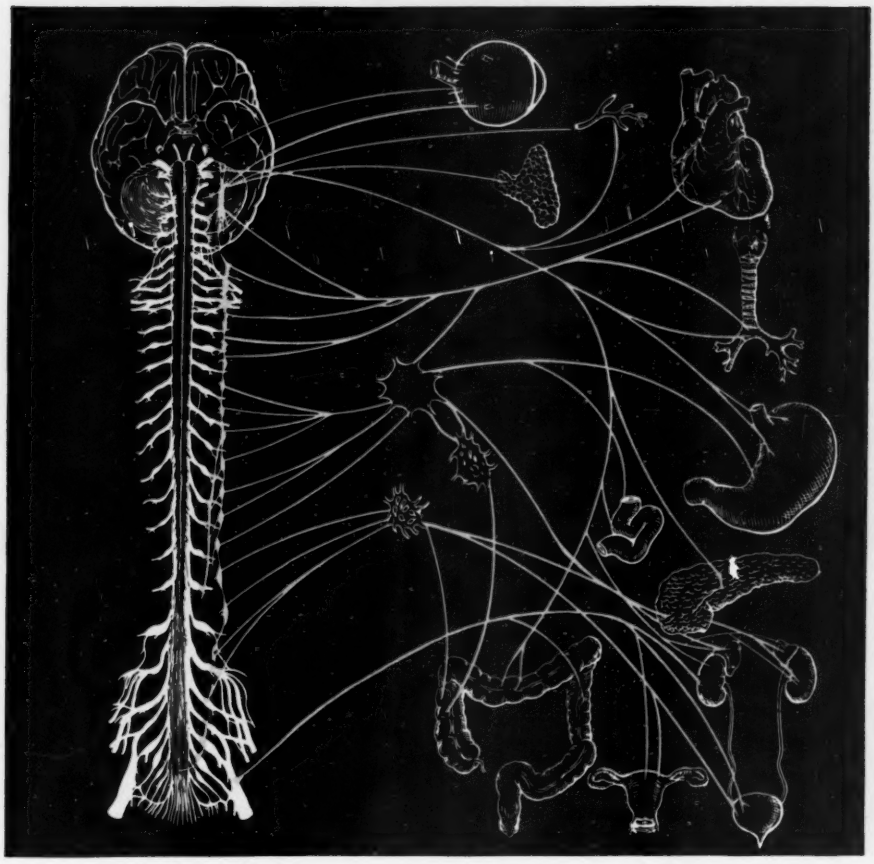
The Committee on Growth of the National Research Council, acting in an advisory capacity, makes recommendations to the American Cancer Society concerning the administration of the grants-in-aid and fellowship portions of the Society's research program. This book, which is the fifth annual report, tells the fascinating story of how the Committee on Growth goes about its business of selecting fellows for training in cancer research and research projects for support by the American Cancer Society. The report is written in a simple and clear style and should be read by all who are interested in cancer research or in supporting it financially. The first part of the report consists of a well-reasoned and pertinently illustrated account of the fellowship program, the grants for scholars in cancer research, the selection of cancer research projects, the distribution of grant-in-aid funds, the participating institutions, and the work of the sections of the Committee on Growth: biology, biochemistry, chemotherapy, clinical investigations, and biophysics. The last section of the book contains detailed summaries of the fellowship and grant projects which will be of interest principally to workers in special fields of cancer research.

These reports are models of their kind and show how a great voluntary public health agency can set up its research program with breadth of view, integrity, and wisdom. Those who read it will derive pleasure and profit for their efforts.

Selected Writings of Sir William Osler, 12 July 1849 to 29 December 1919. Edited by a Committee of the Osler Club of London, with the help of Dr. W. W. Francis. Introduction by Dr. G. L. Keynes. Price, $4. Pp. 278, with 5 illustrations. Oxford University Press, 114 5th Ave., New York 11, 1951.

The sixteen essays selected for republication comprise a delightful mixture of Osleriana and should be particularly appealing to medical students.

The volume is well printed, well indexed, and well illustrated. Every medical school library should own a copy and should tempt students to read it; it is the kind of book, too, for doctors to read on trains or at night or when they wish to be uplifted by Dr. Osler's philosophy and way of life.



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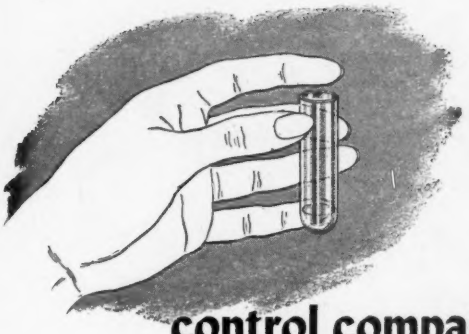

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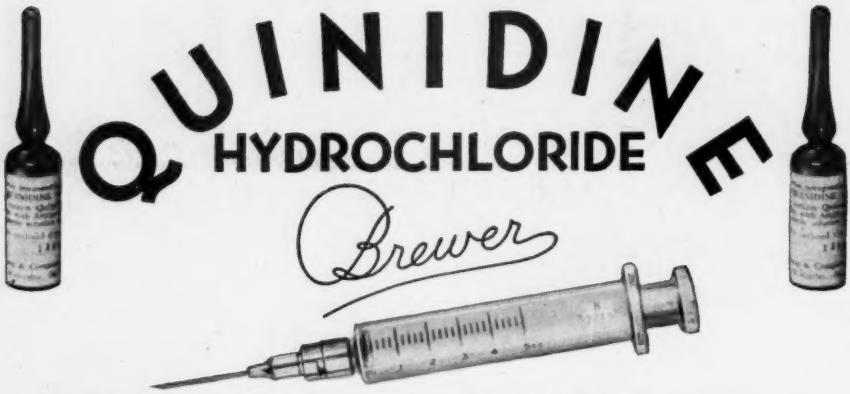

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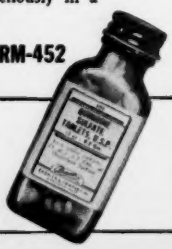

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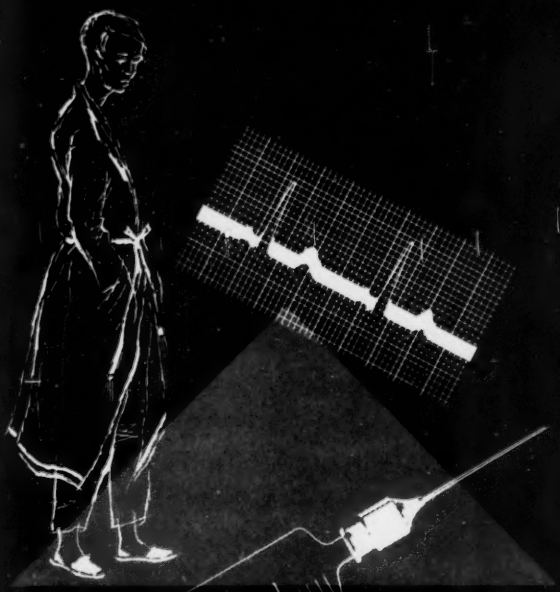

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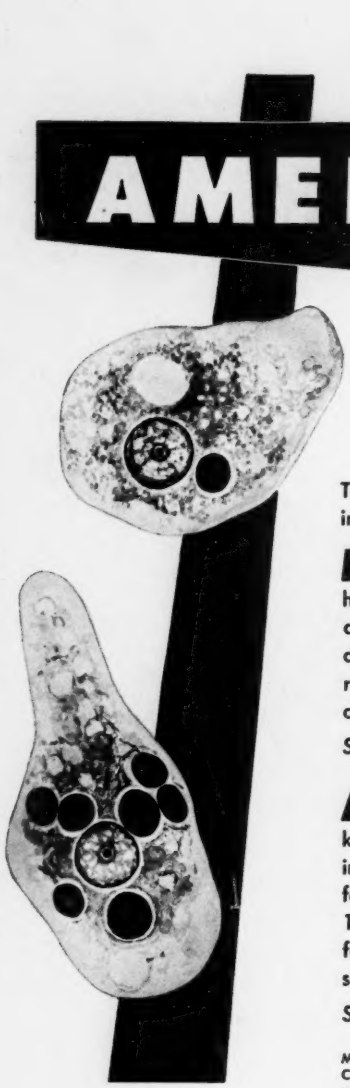

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